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ARCHIVES OF SURGERY

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GUIDE TO REPLACEMENT THERAPY FOR LOSS OF BLOOD OR PLASMA

HILGER PERRY JENKINS, M.D.

PAUL W. SCHAFER, M.D.
AND
FREDERICK M. OWENS JR., M.D.
CHICAGO

The efficacy of transfusion of blood and plasma for relief of shock has become well established. An important problem in replacement therapy is the amount of blood or plasma which is necessary for the individual patient. This depends primarily on two factors: (1) the amount of blood and/or plasma which was originally lost or which continues to be lost subsequent to the shock stimulus or as a result of additional shock stimuli, and (2) the extent to which the compensatory mechanisms of the body, such as vasoconstriction and hemodilution, can make up for the deficiency in blood volume. (Vasoconstriction attempts to adjust the size of the vascular bed to the remaining blood volume, and hemodilution endeavors to replace the loss of whole blood or plasma with tissue fluids.)

The effectiveness of the compensation for a reduction in blood volume depends to a large extent on the original condition of the patient as well as on associated injuries or subsequent therapeutic procedures. Dehydration renders the dilution mechanism less effective. Anemia places a limitation on the extent to which the body will tolerate loss of red cells, and hypoproteinemia may diminish the amount of loss of plasma which can be tolerated. An associated injury to the spinal cord or a subsequent spinal anesthesia will impair the vasoconstrictive mechanism in its attempt to render more effective such blood volume as is available for circulation.

The complete evaluation of the replacement requirements of any one patient requires: (1) measurement of the blood volume, (2) estimation of the efficiency of the vasoconstrictive mechanisms and (3) analysis of the composition of the blood. Methods of determining blood volume are available for clinical use [1] but as yet require equipment not generally available in most hospitals. No reliable test for the efficiency of the vasoconstrictive mechanism has been worked out as yet, although utilizing direct examination of the blood vessels of the conjunctiva by a technic worked out by Knisely [2] may have possibilities. Much of the information which can guide one in the therapy of shock has to do with the composition of the blood. Considerable attention to this aspect has been drawn by Scudder.[3]

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Chicago.

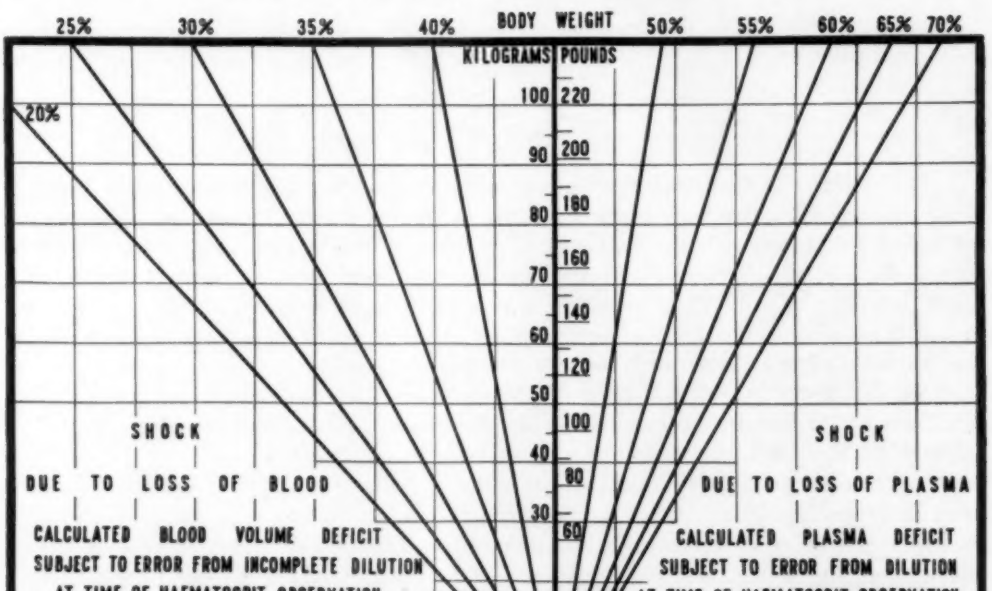
1. Schafer, P. W.: Blood Volume Studies: A Review, to be published.

2. Knisely, M. H., and Bloch, E. H.: Microscopic Observation of Intravascular Agglutination of Red Cells and Consequent Sludging of the Blood in Human Diseases, Anat. Rec. **82**:34, 1942; personal communication to the author.

3. Scudder, J.: Shock: Blood Studies as a Guide to Therapy, Philadelphia, J. B. Lippincott Company, 1940.

The most reliable index of the relative cell content of the blood is the hematocrit reading, or value for cell volume. The hematocrit provides an estimation of the extent to which dilution of the cellular elements of the circulating blood has occurred after loss of whole blood or the extent to which the blood has become concentrated after loss of plasma. From this information one can estimate the approximate deficit in blood volume. In some cases it may also be desirable to take into consideration the protein content of the plasma.

Various methods of estimating replacement requirements for shock due to loss of plasma have been devised. The formula of Harkins [4] is relatively simple and is widely used. The formula of Elkinton, Wolff and Lee [5] and the chart of Wolff and Lee [6] offer a more complete analysis of the replacement requirements. The



To determine requirements for replacement of blood or plasma follow the diagonal line of the hematocrit reading to the point where it intersects the horizontal line of the patient's body weight, in either kilograms or pounds; then follow the vertical line down to the calibration of the required amount of blood or plasma on the bottom line of the chart.

methods of Black [7] and of Berkow [8] also deserve mention. These methods were designed principally for shock due to burns.

4. Harkins, H. N.: The Treatment of Burns, Springfield, Ill., Charles C Thomas, Publisher, 1942.

5. Elkinton, J. R.; Wolff, W. A., and Lee, W. E.: Plasma Transfusion in the Treatment of Fluid Shift in Severe Burns, Ann. Surg. **112**:150, 1940.

6. Wolff, W. A., and Lee, W. E.: A Simple Method for Estimating Plasma Protein Deficit After Severe Burns, Ann. Surg. **115**:1125, 1942.

7. Black, D. A. K.: Treatment of Burn Shock with Plasma and Serum, Brit. M. J. **2**:693, 1940.

8. Berkow, S. G.: A Method of Estimating the Extensiveness of Lesions (Burns and Scalds) Based on Surface Area Proportions, Arch. Surg. **8**:138 (Jan.) 1924.

In an attempt to furnish a simple guide to replacement therapy in shock due to loss of blood or loss of plasma the accompanying chart was constructed. It is based primarily on the hematocrit value and the body weight, the two variables which can be most easily determined under emergency conditions. The normal total blood volume was considered to be two twenty-fifths of the body weight in the light of clinical observations made by one of us (P. W. S.). The normal hematocrit reading was taken to be 45 per cent. Readings below 45 per cent reflect the extent to which the blood volume has been depleted by loss of whole blood and is being replaced by withdrawal of tissue fluids into the circulation. On the other hand, readings above 45 per cent reflect the extent to which the blood volume has been depleted by loss of plasma with resulting hemoconcentration.

When blood is lost, as in hemorrhage or by formation of a hematoma, the process of hemodilution may be slow. Therefore, the original hematocrit reading may not yet reflect the extent to which the blood has been depleted. Consequently the total amount of blood indicated on the chart on the basis of that hematocrit reading may be less than the amount which was originally lost and hence may not be adequate for complete replacement therapy. It does, however, constitute at least a good start toward adequate replacement. Subsequent hematocrit determinations after further dilution has occurred permit correction of the total amount of blood required for complete replacement.

In regard to the amount of plasma which is necessary after loss of plasma, as in burns, crushing injuries or contusions of soft tissues, the hematocrit readings also represent the minimum requirements, because any error on the part of the hematocrit in depicting the deficit in blood volume is due to dilution of the residual plasma by protein-poor tissue fluids. Therefore, for any given hematocrit reading above 45 per cent, regardless of the extent of dilution by tissue fluids, the chart indicates the minimum amount of plasma which will be required for replacement. In such a situation replacement by this amount of plasma of normal protein content at least represents a start toward adequate replacement, and subsequent hematocrit determinations will guide one in estimating the full requirements of plasma in the event of appreciable dilution of the residual plasma. Determinations of the protein content of the plasma are of additional help in estimating the deficit of protein. When facilities are available for such tests, one may make corrections in plasma requirements such as are presented in the chart devised by Wolff and Lee.

When both whole blood and plasma are lost, as in severe fractures or in burns complicated by hemorrhage, the hematocrit reading will not reflect the total deficit in blood volume to the same extent as when the preponderate loss is either blood or plasma. However, for deviations of the hematocrit value below or above 45 per cent that may be observed in such circumstances the chart still indicates the least amount of whole blood or plasma which will be appropriate for replacement. When subsequent changes in the hematocrit reading occur during the course of compensation or treatment, one may then make corrections in the estimate of the total replacement requirements until such time as the hematocrit value becomes relatively stable at 45 per cent.

SUMMARY

This guide to replacement therapy is presented as a simple means of evaluating the *minimum* requirements of blood or plasma for a patient who has suffered loss of blood or loss of plasma. It should be of particular value during the earlier phase of deficiency in blood volume, when clinical symptoms of shock have not as yet appeared.

950 East Fifty-Ninth Street.

LIGATION OF THE SAPHENOUS VEIN FOR VARICOSE VEINS

CAPTAIN R. W. POSTLETHWAIT
MEDICAL CORPS, ARMY OF THE UNITED STATES

In a time such as the present, with the entire resources of the nation mobilized for the successful conduct of war, it is particularly important that elective operations for the persons constituting the nation's manpower result in a maximum number of cures. Varicose veins of the lower extremities cannot be considered a major cause of disability,[1] but the impairment of efficiency of soldiers and workmen afflicted with them is readily apparent.

Even in a small station hospital such as this, patients are seen too frequently with recurrent or inadequately treated varicose veins. In many of the cases it is obvious that if a systematic examination and a proper plan of treatment had been followed a much more satisfactory result could have been obtained. Despite the numerous excellent papers which have been written on this subject,[2] the correct use and technic of ligation of the saphenous vein do not appear to be widely enough understood. Any surgeon who has had occasion to religate the saphenous vein at the saphenofemoral junction only a few months after the first operation can readily appreciate this.

The purpose of this discussion is not to review the pathogenesis, the physiology or the treatment of varicose veins, but is solely to emphasize the importance of proper technic for ligation of the saphenous vein. The tests for determining the competence of the saphenous valves at the fossa ovalis and for locating incompetent communicating veins are described in standard surgical textbooks.[3] The tests used at this hospital are the Trendelenburg, Schwarz, Perthes, Harkins[4] and Ochsner-Mahorner.[5] Depending on the results, ligation at the saphenofemoral junction alone may be indicated, or a more extensive operation with multiple

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From the Surgical Service, Station Hospital, Fort Myer, Va., Col. M. F. DuFrenne, Surgeon.

1. Of 19,923 registrants examined by Selective Service local boards, 531 had varicose veins, an incidence which represents a defect rate of 26.7 per thousand examined (Rowntree, L. G.; McGill, K. H., and Folk, O. H.: Health of Selective Service Registrants J. A. M. A. **118**:1223 [April 4] 1942).

2. Recent papers include: Barrow, W.: Physiologic Changes Associated with Varicose Veins and Their Correction, Arch. Surg. **45**:633 (Oct.) 1942. Harkins, H. N., and Schug, R.: The Surgical Management of Varicose Veins: Importance of Individualization in the Choice of Procedure, Surgery **11**:402 (March) 1942. Moore, S. W., and Knapp, G. M.: Varicose Veins, Ann. Surg. **115**:131 (Jan.) 1942. Payne, R. T.: The Scope of Operation in the Treatment of Varicose Veins, Brit. M. J. **2**:533 (Oct. 18) 1941. Sherman, R. S.: Varicose Veins: A Suggested Operative Procedure, California & West. Med. **57**:192 (Sept.) 1942. Symposium on Varicose Veins, Proc. Staff Meet., Mayo Clin. **16**:820 (Dec. 24) 1941.

3. Ferguson, L. K.: Surgery of the Ambulatory Patient, Philadelphia, J. B. Lippincott Company, 1942. Christopher, F.: Minor Surgery, Philadelphia, W. B. Saunders Company, 1938.

4. Harkins, H. N.: Individualization in the Surgical Treatment of Varicose Veins, Ann. Surg. **113**:1109 (June) 1941.

5. Mahorner, H. R., and Ochsner, A.: The Modern Treatment of Varicose Veins as Indicated by the Comparative Tourniquet Test, Ann. Surg. **107**:927 (June) 1938.

incisions for perforating veins may be required. But regardless of the extent of the operation, it is of primary importance that a standardized procedure be followed in ligating the proximal portion of the great saphenous vein.

Inadequate ligation is indicated by the finding of : (1) a palpable dilated vein at the fossa ovalis, (2) a positive result of the Trendelenburg test, (3) emptying of the dilated veins when the patient walks with a tourniquet at the fossa ovalis, (4) a small cutaneous incision and (5) most conclusively, an intact saphenous vein or dilated tributary at operation. If the foregoing evidences are present, it appears that at the first operation only the saphenous vein or a large tributary mistaken for it was ligated.

Three constant tributaries of the great saphenous vein near the fossa ovalis are usually described. These are the superficial iliac circumflex, the superficial epigastric and the superficial external pudendal vein. The medial and lateral superficial femoral veins are inconstant tributaries. Great variation in the number, size and location of the tributaries is known to occur. In my cases during the past few months, I have attempted to diagram accurately these variations, and even in the small number which I have recorded the extent of variation is marked. It is therefore my feeling that three requirements must be fulfilled before a complete ligation is done: (1) The great saphenous vein must be ligated close to the

Fig. 1.—Ligated lateral superficial femoral vein which was mistaken for the great saphenous vein.

femoral vein; (2) a segment of vein at least 5 cm. in length must be removed, and (3) all tributaries in this segment must be separately ligated. If this is not done, a continuation or recurrence of the incompetency of the saphenous system at the fossa ovalis must be expected.

From the diagrams, it can be seen that if a small incision is made and the first large vein encountered is ligated, the main trunk or a large connecting tributary may be missed. This, of course, will result in failure to stop the backflow. For this reason, an arbitrarily selected length of 5 cm. of vein is removed and all tributaries ligated. The ligation should be close to the femoral vein, not only to decrease the possibility of thrombus formation with resultant embolism, but to avoid overlooking a tributary which empties at or near the saphenofemoral junction and connects with the saphenous vein below the incision in the middle or lower portion of the upper part of the leg. Heyerdale and Stalker [6] state: "This is a situation which we have seen often and is perhaps the most frequent cause of recurrence following operation on the incompetent great saphenous vein."

The procedure is briefly as follows. After preparation of the skin and infiltration with procaine hydrochloride, an oblique incision from 4 to 5 cm. in length is

6. Heyerdale, W. W., and Stalker, L. K.: The Management of Varicose Veins of the Lower Extremities, Proc. Staff Meet., Mayo Clin. **16**:827 (Dec. 24) 1941.

made, located parallel with and approximately 3 cm. below Poupart's ligament and with the lateral end over the femoral pulsation. (The incision is intentionally placed below the fossa ovalis, as moderate retraction will permit excellent exposure of this opening and such an incision will also permit the dissection to be carried more

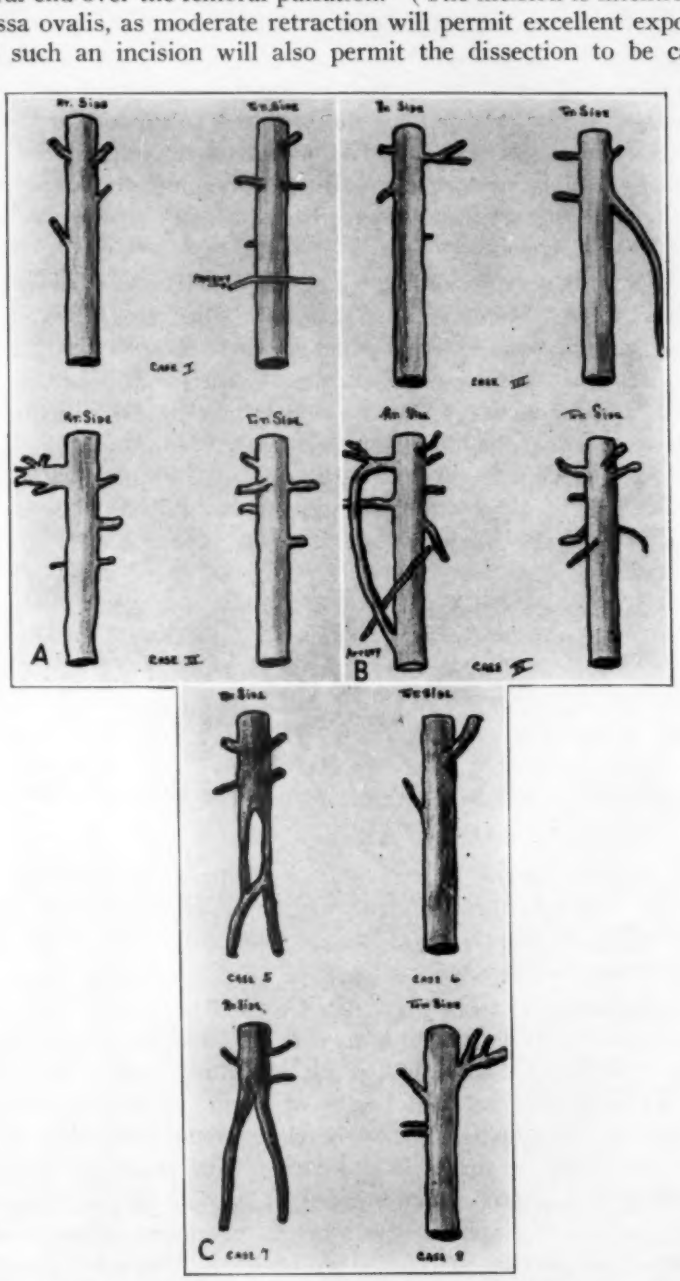

Fig. 2.—*A*, the length of vein diagramed is roughly equivalent to the segment of vein removed at operation (7 or 8 cm.). The upper end is about 0.5 cm. from the femoral vein. *B*, the right side view for case 4 demonstrates how the backflow may continue through a connecting vein if the saphenous vein alone is ligated. *C*, cases 5 and 7 show how the ligation of one trunk may leave another tributary and therefore have no effect on the incompetence.

distally.) The incision is carried down through the superficial fascia, where the great saphenous vein is found lying above the superficial layer of the deep fascia

(fascia lata) and usually in the medial half of the incision. The vein is isolated and divided between clamps. The dissection is carried superiorly to the saphenofemoral junction, each tributary being isolated, divided and ligated before the next is attacked. At the saphenofemoral junction, the saphenous vein is ligated as close as possible to the femoral vein, first with a single silk ligature and then with a transfixion suture of the same material. The portion of the vein distal to the ligature is excised. The dissection is then carried inferiorly, and by upward traction on the vein and downward traction on the edge of the wound a total of 5 to 8 cm. of vein is excised. A single ligature is placed about the inferior end of the vein. Enlarged lymph nodes should be avoided because of the oozing which occurs unless such a node is removed completely. At times a small artery (superficial external pudendal) may be found crossing the vein and this may be ligated if necessary. The superficial fascia and skin are closed with interrupted sutures of fine silk and a firm dressing applied.

The patient is urged to walk as soon as possible after the operation, and if necessary is helped to walk before six hours has elapsed. Walking is then required every seven hours.

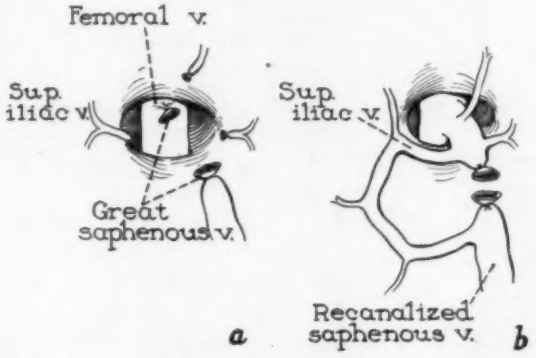

Fig. 3.—Diagrammatic appearance of: (*a*) proper ligation of the saphenous vein and its usual tributaries; (*b*) improper ligation of the great saphenous vein with disregard of its tributaries. The development of collateral circulation through the intact tributaries results in recanalization. (Figures 1 and 3 reproduced by permission of Drs. W. W. Heyerdale and L. K. Stalker.[6])

Retrograde injection of sclerosing solution at the time of operation has been suggested by several authors, but I have not done it because (1) adequate thrombosis of the long saphenous system will occur occasionally after operation without injection, (2) leakage of the solution into the wound may result in unsatisfactory healing and (3) the resulting reaction in a patient sensitive to the sclerosing solution may cause prolonged incapacity.

SUMMARY

In the treatment of varicose veins of the lower extremities, ligation of the great saphenous vein at the fossa ovalis is an important part of the therapeutic plan. If success is to be expected, a complete operation must be done. This will include ligation of the saphenous vein close to the femoral vein, excision of at least 5 cm. of the saphenous vein and ligature of all tributaries of the excised segment.

Station Hospital, Fort Myer.

SARCOMA OF THE STOMACH

A CLINICAL AND PATHOLOGIC STUDY

CAPTAIN GEORGE F. SCHROEDER
MEDICAL CORPS, ARMY OF THE UNITED STATES
AND
HERBERT J. SCHATTENBERG, M.D.
SAN ANTONIO, TEXAS

In recent years there has been a considerable increase in the number of reports of cases of sarcoma of the stomach. It is the purpose of this study to add several cases to the literature and emphasize some of the pathologic features of the disease. The term "primary lymphosarcoma of the stomach" is confusing and requires clarification. It is generally agreed that lymphosarcoma is a systemic disease which may manifest itself in many different ways. If it appears in the stomach this is merely the site of local involvement. Unlike carcinomatous lesions, which form more or less definite patterns depending on the organ involved, lymphosarcoma is essentially the same regardless of the tissue in question. Like carcinoma it is malignant and spreads by continuity and contiguity and metastatically.

Morgagni [1] first described the condition in 1751. Sibley [2] in 1856, Bruch [3] in 1847 and Cruveilhier [4] in 1871 each reported cases. Virchow,[5] in 1887, was the first surgeon to operate on a patient with gastric sarcoma. Fenwick,[6] in a review of the subject, collected 60 cases reported up to 1900. He believed that in 53 of these the diagnosis was adequately proved. In 1913 Flebbe,[7] basing criteria on autopsy observations, collected 157 cases. Forni,[8] in the same year reported a collected series of 200 cases. In 1920 Haggard [9] listed 244 cases, in 107 of which an operation was performed. D'Aunoy and Zoeller [10] reviewed the literature in 1930, bringing the total to 335 cases. Madding [11] stated that 428 cases had been reported up to 1938. The considerable increase in reported cases in recent years must be attributed to better clinical and pathologic standards of diagnosis. This increase is further illustrated in that D'Aunoy and Zoeller [10] reported 4 cases from the records of the Charity Hospital of Louisiana at New Orleans for the period 1906 to 1929. In the same institution during the period 1929 through 1942 there were 9 cases in which the diagnosis was proved by histologic study.

From the Departments of Surgery and Pathology, Tulane University, and the Charity Hospital of Louisiana.

1. Morgagni, cited by Hubeny and Delano.[30]
2. Sibley, S. W.: Example of Multiple Fibrous Tumors, Tr. Path. Soc. London **7**: 340, 1856.
3. Bruch, C.: Die Diagnose der bösartigen Geschwülste, Mainz, V. von Zabern, 1847.
4. Cruveilhier, cited by Forni.[8]
5. Virchow, cited by D'Aunoy and Zoeller.[10]
6. Fenwick, W. S.: Primary Sarcoma of the Stomach, Lancet **1**:463, 1901.
7. Flebbe, G.: Ueber das Magensarkom, Frankfurt. Ztschr. f. Path. **12**:311, 1913.
8. Forni, G.: Contributo allo studio del sarcoma primitivo della stomaco, Riforma med. **30**:624, 1914.
9. Haggard, W. D.: Sarcoma of the Stomach, Surg., Gynec. & Obst. **31**:505, 1920.
10. D'Aunoy, R., and Zoeller, A.: Sarcoma of the Stomach: Report of Four Cases and Review of the Literature, Am. J. Surg. **9**:444, 1930.
11. Madding, G. F.: Lymphosarcoma of the Stomach with Particular Reference to the Reticulum Cell Variety, Proc. Staff Meet., Mayo Clin. **14**:202, 1939.

Gastric sarcoma is generally agreed to constitute about 1 per cent of all malignant gastric tumors. Madding,[11] Ewing,[12] Pack and McNeer,[13] Hesse[14] and many others have cited this percentage. Mars and Kirshbaum[15] reported an incidence of 1.5 per cent and Yates[16] one of 2 per cent. From 1906 through 1941, 13 cases in which the diagnosis was proved were collected from the records of the Charity Hospital. Since in this same period malignant gastric lesions totaled 1,313, 0.99 per cent of these were sarcomas. The diagnosis of sarcoma of any variety or location was made in 1,373 instances. In 0.94 per cent of these cases the lesion was gastric.

The age incidence varies considerably. Chout[17] reported a case he believed to be one of congenital lymphosarcoma of the stomach. Hunt[18] operated on a 3 year old child with this disease, and Finlayson[19] described the lesion in a 3½ year old child. The oldest patients reported on were Grosset's,[20] who was 85 years old, and di Giacomo's,[21] who was 91. D'Aunoy and Zoeller[10] cited the average age in their collected series as 41.6 years. Pack and McNeer[13] found the average age to be 46 years, while Taylor[22] found it to be 44.3 years. It is obvious, therefore, that the disease may appear at any age but that in general it is a disease of middle age, usually affecting persons a decade younger than the average patient with carcinoma.

The majority of reports emphasize a predominance in males (Taylor,[22] D'Aunoy and Zoeller,[10] Pack and McNeer.[13] Hochmann[23] stated that there is no difference in the sex incidence. Of the patients in our series of 9 cases, 4 were males and 5 females.

The cause of sarcoma of the stomach is not known. There has been no recent work to enlighten this phase of the disease.

The clinical picture varies considerably with the location of the lesion, its size and the presence or absence of ulceration and infection. Pain, which is often of the ulcer type, is the most common complaint. Epigastric pressure may be an early symptom, and frequently the first indication of the disease is the presence of an epigastric mass. A palpable tumor is present in 30 to 40 per cent of the cases. Nausea, vomiting, anorexia, loss of weight and weakness develop rapidly. The lesions seldom bleed, but tarry stools are occasionally noticed. Massive hemorrhage and perforation are rare. The presence of generalized lymphadenopathy indicates systemic involvement. Often low grade fever accompanies the condition but it is seldom of the Pel-Ebstein type until late in the course of the disease.

The diagnosis can be made only by microscopic examination. There are no characteristic symptoms, signs or laboratory data that justify a positive diagnosis. Haggard[9] stated that hematemesis in a young person with or without severe pain

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12. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940.
13. Pack, G. T., and McNeer, G.: Sarcoma of the Stomach: A Report of Nine Cases, Ann. Surg. **101**:1206, 1935.
14. Hesse, O.: Das Magensarkom, Centralbl. f. d. Grenzgeb. d. Med. u. Chir. **15**:550, 1912.
15. Mars, M., and Kirshbaum, J. D.: Leiomyosarcoma of the Stomach with Perforation, Am. J. Roentgenol. **44**:716, 1940.
16. Yates, J. L.: Sarcoma and Myoma of the Stomach, Ann. Surg. **44**:550, 1912.
17. Chout, L. K.: Primary Sarcoma of the Stomach, Radiology **34**:714, 1940.
18. Hunt, V. C.: Partial Gastrectomy for Lymphosarcoma in Childhood, Ann. Surg. **96**:210, 1932.
19. Finlayson, J.: Case of Sarcoma of the Stomach in a Child Aged Three and One-Half Years, Brit. M. J. **2**:1535, 1899.
20. Grosset, L. L.: Le sarcome primitive de l'estomac, Presse méd. **22**:221, 1912.
21. di Giacomo, G.: Su due casi di sarcoma primitivo dello stomaco, Riforma med. **31**: 114, 1915.
22. Taylor, E. S.: Primary Lymphosarcoma of the Stomach, Ann. Surg. **110**:200, 1939.
23. Hochmann, A.: Sarcoma of the Stomach, Lancet **1**:362, 1940.

and a palpable tumor mass without obstruction may signify gastric sarcoma. Ritter [24] expressed the opinion that patients between 20 and 35 years of age with a large gastric neoplasm are more likely to have sarcoma than carcinoma. Indeed, these two conditions are frequently confused, and histologic examination of tissue from a patient operated on with a tentative diagnosis of carcinoma often proves the disease to be sarcoma. The gastric analysis varies with the location and extent of the lesion. A hypochromic, macrocytic anemia is the rule. Roentgenograms are not diagnostic. Several abnormalities of the rugae have been described, but as Chout [17] and Archer and Cooper [25] pointed out, these are merely indications. Chout [17] described flat tumors with smooth borders, pedunculated growths, isolated filling defects on the greater curvature with deep indentation or with a crater shadow in it and tumors on the greater curvature side of the fundus as suggestive of sarcoma. A number of writers have agreed with Schindler [26] that gastroscopic examination is an aid. In any event one must not hesitate too long to advise exploration when it is suspected that an ulcer or tumor in a patient of any age may be a malignant neoplasm. Time is just as important for the successful treatment of sarcoma as in that of carcinoma.

The pathologic classification of sarcoma in general has been and is still somewhat confusing. Ewing [12] mentioned three types when discussing gastric sarcoma:

1. Spindle cell myosarcoma
2. Miscellaneous round cell or mixed cell alveolar sarcoma
3. Lymphosarcoma
   (*a*) Reticulum cell
   (*b*) Malignant lymphosarcoma (small round cell)

Pack and McNeer [13] in a recent paper clarified the problem further in an excellent table in which they described the histogenesis and the site of the lesion and the symptoms. They listed three main types:

1. Spindle cell sarcoma
   (*a*) Neurosarcoma
   (*b*) Myosarcoma
2. Lymphosarcoma
   (*a*) Primary
   (*b*) Generalized lymphosarcomatosis
3. Miscellaneous round cell or alveolar sarcoma; metastatic sarcoma, such as melanoma

They expressed the opinion that most so-called primary lymphosarcomas are of the reticulum cell type, and that relatively few, if any, are of the malignant lymphocytoma variety. Madding and Walters,[27] following Ewing's basic classification, differed in that they found an equal distribution of the two types. In addition these authors described cases of Hodgkin's sarcoma, leiomysarcoma, fibrosarcoma and a mixed type. Roulet [28] described a tumor he called retotheliosarcoma, and Edling [29] pointed out that this is the same as reticulum cell lymphosarcoma.

24. Ritter, S. A.: A Case of Primary Lymphosarcoma Occupying Two-Thirds of the Fundus of the Stomach, Am. J. Surg. **47**:131, 1940.

25. Archer, V. W., and Cooper, G.: Lymphosarcoma of the Stomach: Diagnosis and Treatment, Am. J. Roentgenol. **42**:332, 1940.

26. Schindler, R.: Gastroscopy, Chicago, University of Chicago Press, 1937.

27. Madding, G. F., and Walters, W.: Lymphosarcoma of the Stomach, Arch. Surg. **40**:120 (Jan.) 1940.

28. Roulet, F.: Das primäre Retothelsarkom der Lymphknoten, Virchows Arch. f. path. Anat. **277**:15, 1930.

29. Edling, L.: Contribution to the Pathology and Clinical Picture of Reticulum Cell Sarcoma, Radiology **30**:19, 1938.

Hubeny and Delano [30] coined the term "retothel sarcoma," which is again the reticulum cell type.

Study of the gross pathologic anatomy indicates that the site of the tumor may be exogastric, intramural or endogastric. It may be a diffuse infiltrating lesion or a nodular tumor, or there may be multiple nodules invading all of the gastric wall. Other forms of gastric sarcoma are an infiltrating but limited lesion and a pedunculated, bulky, vascular tumor clearly demarcated from the gastric wall. Ewing [12] expressed the opinion that when the tumor grows beyond its blood supply ulceration results. According to Pack and McNeer,[13] the tumor may invade the submucosa, stretching the mucosa, which then undergoes pressure atrophy and ulceration. Myosarcomas often attain enormous size and are usually subserous in their growth. Pack and McNeer [13] described an exogastric myosarcoma which weighed 3,600 Gm. Such polypoid tumors may be intragastric or exogastric and usually arise on the greater curvature. When exogastric they usually spread between the layers of the great omentum. Brodowski [31] described a tumor weighing 6 Kg. and containing 6 liters of fluid. Neurogenic sarcomas are often, though not always, associated with neurofibromatosis. The gastric lesion is similar in type to neurogenic lesions elsewhere and is often pedunculated or ulcerated and of low grade malignancy. On section the tumors generally are soft and sometimes cystic, with areas of firm, gray or reddish brown tissue and areas of degeneration and hemorrhage.

Madding and Walters [27] discussed the lymphatics of the stomach, which begin in the mucous membrane and extend through to the retroperitoneal glands. There are plexuses in the submucosa where the lymph follicles are situated. The central portion of each one (the secondary follicle) contains less mature lymphocytes. They are typical of lymphosarcoma in general. In reticulum cell sarcoma the lymph follicles are destroyed by large, pale cells with nuclei of bizarre configuration, round, oval or horseshoe shaped. The nucleoli are not prominent, and chromatin is diffusely dusted throughout the nuclear substance. The cytoplasm is eosinophilic. The cellular structure is loose, and small lymphocytes are present. The tumor is infiltrative, and tumor cells may be noted in the blood vessels. The gastric wall is destroyed, and regional metastasis may be present.

The malignant lymphocytoma, or small round cell type, involves the lymphoid tissue by infiltration of immature small lymphocytes. There is little fibrosis and no eosinophilia. Adjacent tissues may be invaded, and there may be an associated lymphatic leukemia.

Myosarcomas vary greatly from those of questionable malignancy, the extremely cellular myomas, to the anaplastic undifferentiated tumors of high malignancy. They are composed of spindle cells arranged in intertwining bundles or of large round cells. The cells may be very long, with finely fibrillar, acidophilic cytoplasm and hyperchromatic nuclei, often extremely large. Ewing [12] expressed the opinion that many so-called angiosarcomas and lymphangiosarcomas fall into this group.

Neurogenic sarcomas of the stomach are similar to those found elsewhere, being classifiable as sclerosing fibrosarcoma, spindle cell neurosarcoma and cellular anaplastic neurosarcoma. The structure may vary in the same tumor but in general the three classes correspond to the rate of growth.

The miscellaneous round cell or alveolar sarcoma tends toward alveolar grouping of the cells in some areas, while elsewhere the cells are scattered uniformly through-

30. Hubeny, M. J., and Delano, P. J.: Retothel Sarcoma of the Stomach, Radiology **34**:366, 1940.

31. Brodowski, W.: Ein ungeheures Myosarkom der Magens nebst secundären Myosarkomen der Leber, Virchows Arch. f. path. Anat. **67**:227, 1876.

out the tissue and separated by a delicate stroma in which may run numerous small, thin-walled blood vessels.

In reality a sarcoma is a malignant tumor of connective tissue. Strictly speaking, then, malignant tumors of muscle, lymphoid tissue and pigment cells have no place in the classification. It has been the general custom, however, to include such tumors as lymphosarcoma in this classification, and until a better understanding of the basic tissues is had it seems best to apply clinical findings and past pathologic experiences in making up the grouping of sarcomas.

The prognosis in a case of gastric sarcoma depends entirely on the type of tumor and its location, extent and duration. The differentiated tumors, such as fibrosarcoma, leiomyosarcoma and neurogenic sarcoma, present a better prognosis than the more malignant undifferentiated myoma. A guarded prognosis is, of course, always the best. In general it may be said that the prognosis of sarcoma at the present time is better than that of carcinoma.

Treatment is of three types: surgical removal, irradiation (radium therapy, high voltage roentgen therapy or both) and a combination of operation and irradiation. A positive diagnosis is impossible without biopsy. If after exploration and diagnostic examination of a frozen section it is apparent that the lesion is not resectable irradiation alone should be employed. If the lesion recedes after irradiation, it may be advisable in certain selected cases to resect it at a later date.

REPORT OF CASES

CASE 1.—Mrs. A. T., a white woman 59 years old, was admitted to the Charity Hospital on Oct. 8, 1929, complaining of vomiting blood. On October 5 she had suffered attacks of dyspnea, severe abdominal pain and dizziness. On October 8 vomiting of a cup of blood was followed by a second emesis of a pitcher of blood. She had had frequent attacks of indigestion, constipation, dyspnea and edema of the ankles. No history of melena or loss of weight was recorded.

Examination revealed an extremely ill elderly white woman who appeared definitely anemic and did not respond well to questioning. There was general abdominal tenderness but no palpable mass. The temperature was 100 F., the pulse rate 104, the respiratory rate 22 and the blood pressure 108 systolic and 50 diastolic.

Laboratory studies revealed a red blood cell count of 2,700,000, a white cell count of 5,750 and a hemoglobin content of 55 per cent. The urine was normal, and the Wassermann reaction of the blood was negative.

The patient's course in the hospital was downhill, and she died on October 16.

Autopsy.—On the lateral wall of the stomach 3 cm. below the entrance of the esophagus and lying in the upper border of the greater curvature was an indurated ulcer 5 cm. in diameter. The borders were raised, and protruding from its center was a fungating mass of dirty gray, firm tissue, which divided it into compartments in which was found gray, glistening tissue. The stomach contained a thin, coffee-ground-like material.

The microscopic diagnosis was spindle cell sarcoma.

CASE 2.—L. C., a 39 year old Negro woman, was admitted to Charity Hospital on March 2, 1932, complaining of vomiting. She dated her illness back one year, at which time she noted fulness in the epigastrium following intake of food. Her mouth became sore, and her weight decreased from 135 pounds (61.2 Kg.) to 80 pounds (36.3 Kg.). Dietary treatment by her physician resulted in temporary improvement. In December 1931 vomiting began. This symptom progressed and the stools became watery and frequent, there being three or four a day, but no blood was passed. In February her vagina became sore. At the time of admission to the hospital she was extremely weak.

Examination revealed an emaciated Negro woman who had many dirty ulcerations of all mucous membranes. The blood pressure was 90 systolic and 68 diastolic, the temperature 98.6 F., the pulse rate 86 and the respiratory rate 20. A suggestion of a mass was present in the epigastrium. This mass was not tender and appeared to be movable.

Laboratory studies revealed an erythrocyte count of 3,000,000, a hemoglobin content of 45 per cent and white blood cell count of 7,000 with 60 per cent polymorphonuclear cells. The Wassermann reaction was negative. Gastric analysis showed no free hydrochloric acid

and a total acidity of 62 degrees. A series of roentgenograms of the gastrointestinal tract showed an extensive obstructive lesion in the region of the pylorus with dilatation of the stomach and large six, twenty-four and forty-eight hour gastric residues.

The patient was admitted to the medical ward with a diagnosis of pellagra. The roentgenograms suggested that carcinoma of the stomach was also present, and exploration was carried out. A subtotal gastric resection was done on April 6. The postoperative course was relatively smooth for four weeks, after which it was gradually downhill, with several episodes of psychosis. The patient died on June 27.

The tissue removed at operation consisted of the lower portion of the stomach, including the pyloric ring and the first centimeter of the duodenum. Just above the duodenum was a large ulcerated area, not much raised above the surface. However, the wall of the stomach was considerably thickened and indurated. The lesion was definitely a malignant tumor of the stomach, in a rather early stage, however, and inclined to be self limiting.

The microscopic diagnosis was lymphosarcoma, malignant lymphocytoma type (fig. 1).

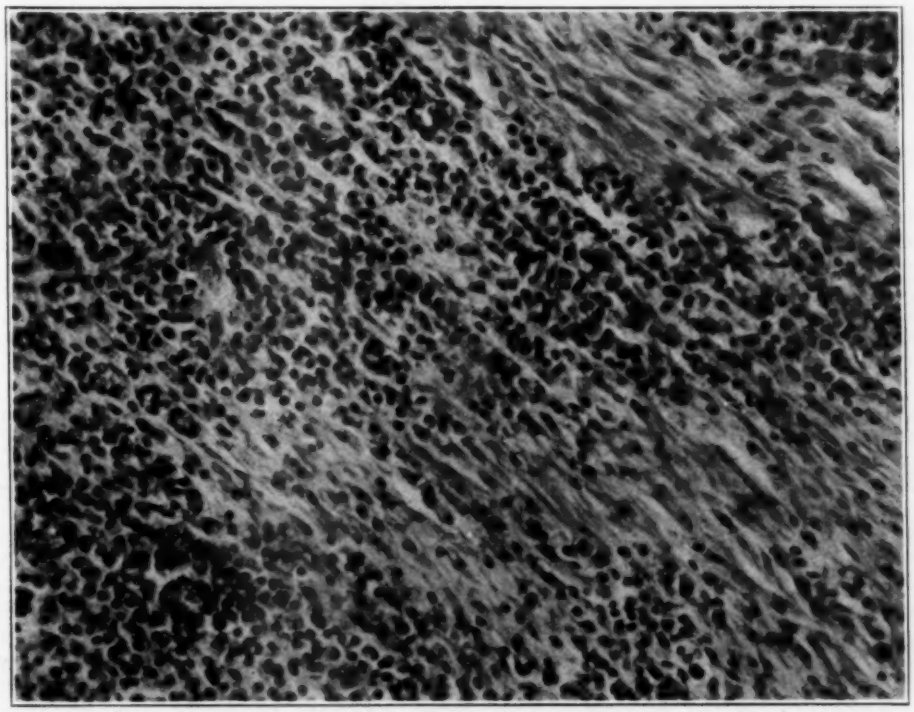


Fig. 1.—Photomicrograph of a section of the wall of the stomach, showing infiltration of muscular layers by neoplastic cells of malignant lymphocytoma, lymphosarcoma type. × 200.

Case 3.—A 50 year old Negro woman was admitted to the hospital on Oct. 10, 1933, complaining of pain in the left side. Five months prior to admission, in May 1933, a colicky pain aggravated by intake of food had developed in the left upper quadrant of the abdomen. The patient's physician tried various medications, but her symptoms were not relieved. He then noted a mass in the left upper quadrant of the abdomen and sent her immediately to the hospital.

On examination it was found that her temperature was normal, pulse rate 85, respiratory rate 20, and blood pressure 160 systolic and 100 diastolic. In the left upper quadrant of the abdomen there was a round mass, 15 by 15 cm., which was hard, movable and nontender and appeared fixed posteriorly.

Laboratory studies revealed an erythrocyte count of 4,325,000, a hemoglobin content of 75 per cent and a white cell count of 8,250. The Wassermann reaction, the blood chemistry and the results of urinalysis and phenolsulfonphthalein determinations were normal. Examination of the patient's stools revealed no blood or intestinal parasites. Roentgenograms of the

kidneys and bladder, including pyelograms, indicated normal conditions. A series of roentgenograms of the gastrointestinal tract demonstrated considerable displacement of the stomach downward, to the left and backward by an extensive tumor which also displaced the transverse colon downward. The most likely site of origin seemed to be the left lobe of the liver, and an amebic abscess was suspected.

When exploration was done on October 18 a tumor was found high in the upper left quadrant of the abdomen. It was adherent to the liver and transverse colon. The pedicle was attached to the anterior wall of the stomach and involved an area about 2.5 cm. in diameter. Excision of the tumor was accomplished, and the patient was discharged on November 10. No follow-up has been possible.

The pathologist's report stated that the specimen consisted of a lobulated tumor mass of bizarre appearance and fairly well encapsulated, although the capsule had been broken in many places, apparently during removal. The origin and anatomic structure of the tumor could not be determined. The tumor mass was extremely friable, and on section some areas were white and slightly firmer than others. Other areas had undergone hemorrhagic degenerative change. The lesion appeared to be a sarcoma.

The microscopic diagnosis was myxosarcoma.

CASE 4.—F. G., a 46 year old Negro man, was admitted to the hospital on Jan. 24, 1934, complaining of a lump in the stomach. In October 1933, the patient began having a feeling of discomfort in the stomach following meals. Home remedies relieved this feeling for a short period, but in November he began having a dull pain. His appetite diminished and he vomited frequently after eating. The vomitus never contained blood. In December he noted a mass in his stomach that was somewhat tender. The mass increased rapidly in size and he completely lost his appetite and became very weak and listless. He also noted occasional tarry stools.

Examination revealed an emaciated Negro man with a large, tender nodular mass extending from under the left costal margin into the upper right quadrant of the abdomen. The mass moved with respiration.

Laboratory studies revealed a red blood cell count of 3,770,000, a hemoglobin content of 55 per cent and a white cell count of 9,000. The Wassermann reaction was negative. Gastric analysis revealed no free acid and a total acidity of 9 degrees. Tests for occult blood gave positive results. A series of roentgenograms of the gastrointestinal tract showed a large tumor involving the prepyloric region of the stomach and the lower portion of the fundus. There was over 50 per cent gastric retention at six hours. The colon showed no evidence of pathologic change.

On Feb. 2, 1934, exploration was done and the lesion was discovered to be an extensive malignant tumor of the stomach with metastasis. Resection was not possible. The patient died on February 22, after a cerebral accident.

Significant observations at autopsy were limited to the brain, where embolism and necrosis had occurred, and to the gastrointestinal tract. The stomach was involved in a large mass of adhesions including the liver and the duodenum. When the stomach was opened a peculiar lesion apparently involving the mucosa was found. The wall of the stomach was not greatly thickened, and there was no induration of the tumor, which was flat. There were small ulcerations over approximately one third of the pyloric portion of the stomach. On the serosal surface of the stomach there were several small nodes which on section were white, watery and glassy and apparently sarcomatous. No further metastatic phenomena could be demonstrated. The duodenum was not involved.

On microscopic examination sections taken through the stomach showed a diffuse infiltration throughout the layers with small round mononuclear and multinucleated cells undergoing all stages of mitosis. The cells were definitely malignant and had the appearance of lymphosarcoma of the malignant lymphocytoma type.

CASE 5.—Mr. C. S., a 58 year old white man, was admitted to Charity Hospital on June 6, 1935, complaining of weakness, which had been gradual in onset over a period of four years. He also noted dyspnea, palpitation, vertigo, and a loss of 17 pounds (7.7 Kg.) in weight in one month. His appetite remained good.

Examination revealed an anemic-appearing man, with a lemon yellow tinge to the skin and evident pallor. The liver was palpable 2.5 cm. below the costal margin.

Laboratory studies revealed an erythrocyte count of 1,955,000 and a hemoglobin content of 45 per cent. Occult blood was present in the stools and gastric contents. Free hydrochloric acid was 53 degrees and total acid 86 degrees. The Wassermann reaction was negative, and the urine was normal. A series of roentgenograms of the gastrointestinal tract showed a prepyloric filling defect in the stomach. There was no six hour gastric residue, and no pathologic changes were observed in the colon.

After adequate preparation a subtotal gastric resection was done, and the patient was discharged in good condition on August 8.

The specimen submitted to pathologic examination consisted of two flat pieces of tissue on a portion of stomach wall with attached mesentery containing fat, which had been previously sectioned. The ulcer measured 1.5 cm. in diameter. It had a smooth surface, and there was considerable induration of the edges. There was a lymph node attached, which on section was smooth and pink.

The microscopic diagnosis was neurosarcoma (fig. 2).

The patient returned on Aug. 25, 1940, complaining of a mass in the abdomen. This was first noted in April and had gradually increased in size. No other symptoms were recorded.

On examination the mass was palpated in the midline at about the level of the umbilicus. It was 15 cm. in diameter, firm and not movable.

Laboratory studies revealed an erythrocyte count of 5,000,000 with a hemoglobin content of 90 per cent. The Wassermann reaction was negative, and the results of urinalysis and of

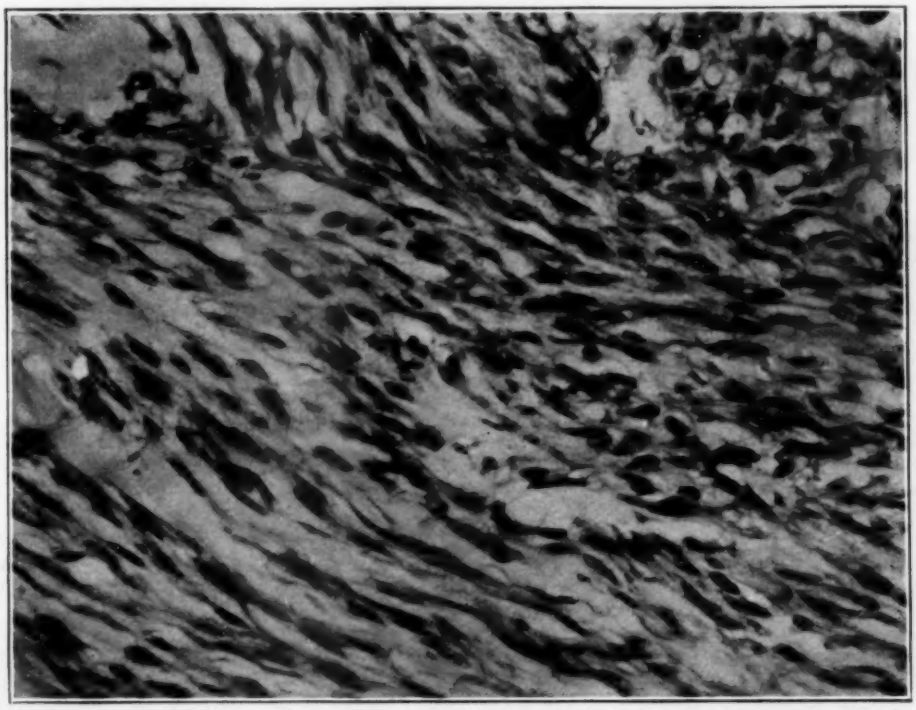


Fig. 2.—Photomicrograph of neurosarcoma of the stomach, showing spindle-like cells with anaplastic, deeply staining nuclei and an ample amount of cytoplasm, in columnar arrangement. × 200.

chemical studies of the blood were normal. Roentgenograms of chest, pelvis and abdomen were negative. A series of roentgenograms of the gastrointestinal tract showed a normally functioning stoma. No evidence of recurrence was noted in the stomach. There appeared to be a large mass displacing the hepatic flexure of the colon downward.

Exploration on September 7 revealed a large tumor mass, approximately 10 cm. in diameter, in the retroperitoneal space. It pushed the transverse colon anteriorly so that it was flattened. By careful dissection the peritoneum over the mass was opened and in an attempt to isolate the tumor a portion of the capsule ruptured. A large amount of degenerated material was evacuated. The capsule was imbricated. The pathologist's report stated that the specimen consisted of a mass of tissue measuring 17 by 11 by 5 cm. It was soft and reddish brown. It was noted that here and there hemorrhages had completely replaced the substance of the tumor. Microscopic examination of the tissue revealed it to be a neurosarcoma similar to the previous growth. The patient made an uneventful recovery and was discharged on September 23. He was to return for some palliative high voltage roentgen therapy, but he failed to do so.

On March 8, 1942 he returned, stating he had been perfectly well until February. At this time he noted several episodes of nausea and vomiting. His abdomen began to swell and became painful. There was considerable loss of weight.

Examination revealed an anemic, poorly nourished white man with a distended abdomen. The abdominal veins were abnormally prominent, and shifting dulness and a fluid wave were present.

Laboratory studies revealed a red cell count of 3,500,000 and a hemoglobin content of 60 per cent. The white cell count was 7,800, with 62 per cent polymorphonuclear cells. The results of urinalysis and of chemical studies of the blood were within the normal range. Roentgenograms of the abdomen and the chest showed no evidence of pathologic conditions. On two occasions paracentesis was done, 1,000 cc. of bloody fluid being removed each time. Examination of this fluid failed to reveal any tumor cells. When the abdomen was flat, it was possible to palpate numerous nodules, some fixed and some movable. It was not deemed advisable to give palliative high voltage roentgen therapy because of the relatively poor response of neurosarcoma to such treatment. The patient was discharged on March 21 to return for additional paracenteses when needed. To the time of writing he has remained fairly comfortable.

CASE 6.—A. W., a 43 year old white man, was admitted to Charity Hospital on June 2, 1936, complaining of pain in the stomach. On May 14, after he had drunk a pint (475 cc.) of cold raw milk, he felt a severe pain in the stomach and his abdomen became distended. Thereafter eating was invariably followed by pain and bloating, relieved at times by sodium bicarbonate. He had not vomited.

Examination revealed a tender, painful abdominal mass about 6 cm. in diameter and movable. There was a small, hard nodule in the subcutaneous tissue just above the umbilicus.

The Wassermann reaction was negative, and the results of urinalysis and of the Aschheim-Zondek test were normal. A series of roentgenograms of the gastrointestinal tract showed an ulcer crater in the prepyloric region of the stomach. At six hours there was no gastric retention, the meal resting in the terminal portion of the ileum and the ascending colon.

On June 16 exploration revealed an extensive carcinoma which infiltrated the entire posterior wall of the stomach from the fundus to the pylorus. It was impossible to resect the lesion. The small nodule in the subcutaneous tissue as well as a portion of the gastric lesion was removed for study. Microscopic examination of this tissue revealed lymphosarcoma, reticulum cell type.

CASE 7.—H. E., a white man 67 years old, was admitted to the Charity Hospital on Oct. 26, 1939, complaining of "stomach trouble." For six months he had been having cramplike pain aggravated by intake of food. Constipation and tarry stools had been noted for a similar period, and there had been a loss in weight of 50 pounds (22.7 Kg.).

Examination revealed an emaciated, elderly white man with a distended, diffusely tender abdomen. The veins over the abdomen were tortuous and prominent. A tender, movable mass 5 cm. in diameter was present in the left lower quadrant. The liver was palpable 10 cm. below the right costal margin and was nodular.

Laboratory studies revealed an erythrocyte count of 3,500,000, a white cell count of 8,500 and a hemoglobin content of 70 per cent. The Wassermann reaction was negative and the results of urinalysis were normal. The icterus index was 14.5. A series of roentgenograms of the gastrointestinal tract showed a constant filling defect in the upper third of the stomach. At the end of six hours there was a trace of gastric retention.

The patient's course in the hospital was downhill, and he died on November 9. At autopsy a large mass, 11 cm. in diameter, was found in the fundus of the stomach. There was extensive infiltration of the entire gastric wall, so that the whole stomach presented considerable thickening, induration and narrowing of the lumen. There was a massive extension of the tumor tissue to the lymph nodes on the lesser and the greater curvature of the stomach, producing several large, extrinsic nodules of the tumor tissue, one of which extended into the notch of the spleen. There were a large nodule of tissue in the inferior surface of the left side of the diaphragm and a similar infiltration on the superior surface, which was not, however, adherent to the inferior surface of the lung. On the anterior surface of the stomach there was a necrotic perforation 1.5 cm. in diameter. The edges were indurated and grayish green.

Microscopic Examination.—Sections through the tumor tissue showed it to be composed of many small round cells lying in a network of skin strands of fibrillar conective tissue. Many of the cells were pointed. The nuclei were round and hyperchromatic and the cytoplasm was scant. Throughout the tumor tissue were scattered a number of larger cells which had large, oval nuclei and homogeneous pink-staining cytoplasm. A number of these cells had irregular nuclei. The impression was that the tumor was a lymphosarcoma of the stomach, malignant lymphocytoma type.

CASE 8.—Miss G. P., a 70 year old white woman, was admitted to Charity Hospital on March 12, 1939, complaining of "hemorrhage from the rectum." The history obtained from her family consisted merely of the statement that she had had a large hemorrhage from the rectum.

Examination revealed a comatose, poorly nourished, elderly white woman. There was edema of the face and lower extremities.

She was given a transfusion of 500 cc. of whole blood but died the day after her admission to the hospital.

At autopsy the stomach contained a large amount of coffee-ground-like material. A nodule measuring 2.5 cm. in its greatest diameter was found in the anterior wall. The mucosa over the nodule was ulcerated and contained a thrombosed vessel. On section the nodule appeared pale gray and soft, except for a small portion which was firm. The heart was enlarged and dilated and there was complete consolidation of the lower lobe of the right lung. Microscopic sections through the neoplasm within the wall of the stomach revealed a whorled mass of spindle-shaped cells

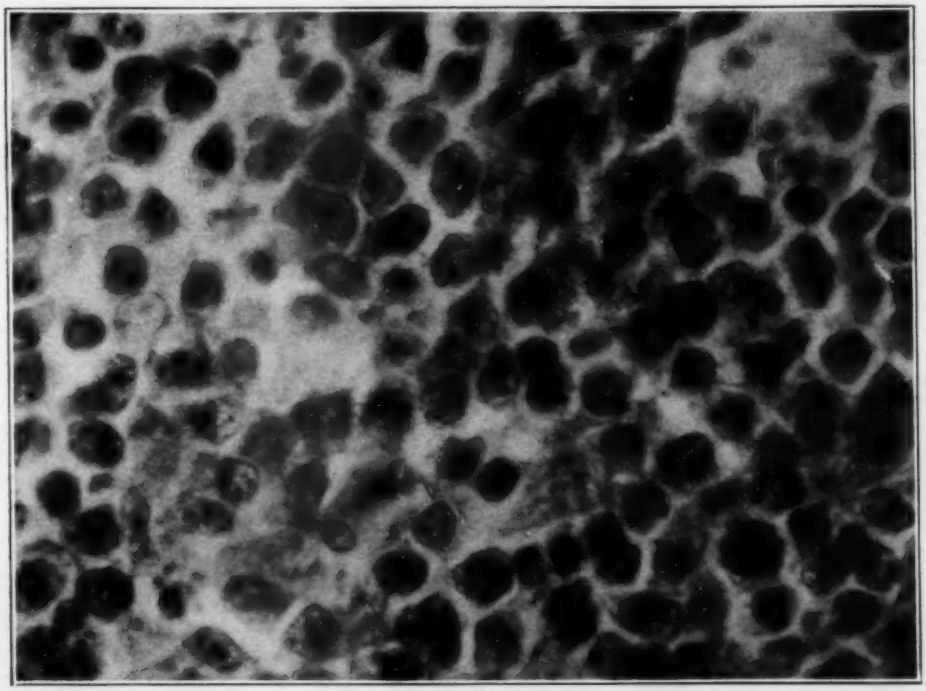


Fig. 3.—Photomicrograph of malignant lymphocytoma, reticulum cell type, of the stomach. The cells are of large size, with prominent, vesicular nuclei, some appearing extremely anaplastic, and scanty amounts of cytoplasm. × 400.

situated within the muscularis. A few figures were present. The impression was that the lesion was a leiomyosarcoma of the stomach.

CASE 9.—W. N., a white man, aged 61 years, was admitted to the hospital on Dec. 29, 1939, complaining of "stomach trouble." In June he noted cramplike pain on eating, associated with vomiting. Later he noticed a small mass in the epigastrium, which gradually increased in size. He never vomited blood or passed blood by rectum.

Examination on admission revealed a cachectic elderly white man, very weak and pale. His abdomen was distended by a large mass. A rectal shelf was palpable.

The patient's course was rapidly downhill. He died on Jan. 5, 1940. At autopsy 2,000 cc. of serosanguineous fluid was found in the peritoneal cavity. The omentum could not be identified as such, for it was completely replaced by a mass of reddish gray, friable nodular tissue. The mesenteric lymph nodes were slightly enlarged, and the cut surfaces showed no neoplastic invasion. The wall of the stomach measured 2.5 cm. in thickness in the pyloric portion. The rugae were absent, and the mucosa was brownish red with gangrenous areas

1 to 2 cm. in diameter. On the anterior surface of the stomach was a mass 15 by 11 by 3 cm., which was reddish gray, firm and friable. The mass and the stomach weighed 1,350 Gm. The rectal wall was infiltrated by similar tissue. The lymph nodes in the region of the stomach were infiltrated with tumor tissue. Microscopically the mucosa of the stomach was infiltrated by lymphocytes. The submucosa and muscularis were infiltrated and had been replaced with tumor cells similar to those found in the tumor mass. The cells were small round cells with scant cytoplasm and large, dark-staining, vesicular nuclei. The connective tissue stroma was extremely scant. A few dilated capillaries traversed the tumor mass. The impression was that the lesion was lymphosarcoma, reticulum cell type.

CASE 10.—Mrs. L. H., a white woman 31 years old, was admitted to Charity Hospital on Jan. 17, 1941, complaining of "vomiting." For six months she had been vomiting, at first only occasionally and later three or four times weekly. She had lost 15 pounds (6.8 Kg.) in this time and had a very poor appetite. For the past two months she had had a dull burning pain behind the sternum.

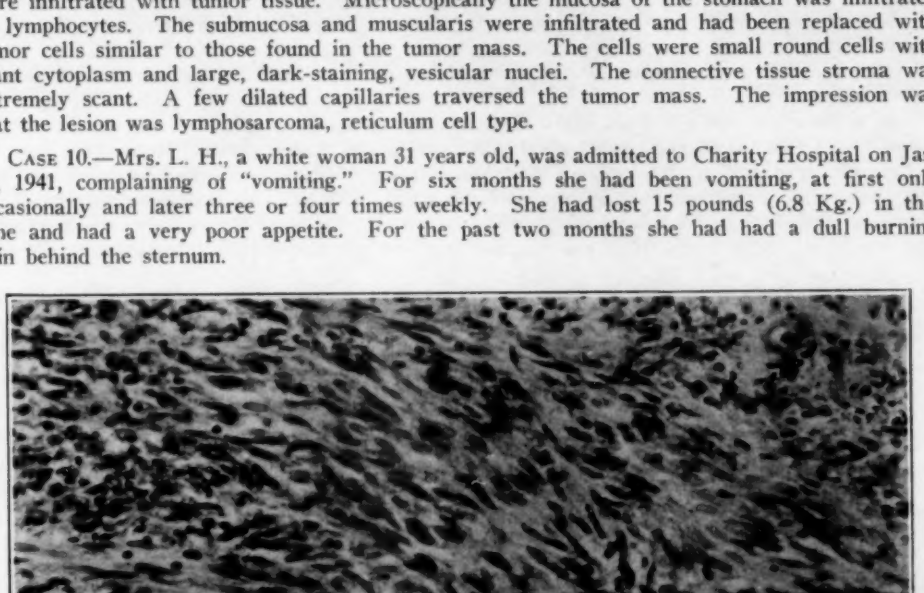


Fig. 4.—Photomicrograph of leiomyosarcoma of the stomach. The cells are spindle-shaped and arranged in whorls. Some are shown cut longitudinally, while others are cut transversely, giving them a spherical appearance. × 200.

On examination she appeared normal except for fairly far advanced emaciation. Complete laboratory studies revealed an erythrocyte count of 4,400,000, with a hemoglobin content of 60 per cent and a white cell count of 10,300. The Wassermann reaction was negative and the results of urinalysis, complete chemical study of the blood, examination of the stools, and determination of the basal metabolic rate were normal. Roentgenograms of the gastrointestinal tract as well as of the chest and skull appeared normal. Gastric analysis revealed achlorhydria.

The patient's course in the hospital was uneventful, with no change in her condition other than relief of the intestinal burning by dietary measures. She was discharged on March 1 and told to return on March 31. She returned on this date to the medical service, where another gastrointestinal roentgenogram was taken, which showed a constant filling defect in the upper two thirds of the stomach. It was thought that the lesion was probably due to carcinoma. A roentgenogram of the chest as well as two Wassermann tests and an electrocardiogram did not afford any evidence of disease. The patient was prepared for operation,

and a total gastrectomy with esophagojejunostomy and enteroenterostomy was performed. It was necessary to remove the spleen because of damage to the splenic artery. Because of the suspected infiltration and adhesions a portion of the left lobe of the liver and the tail of the pancreas were also removed. The postoperative course was stormy, and death from peritonitis occurred on the sixth day, May 2, 1941.

The report on the tissue removed at operation was as follows:

The specimen consisted of a stomach, a spleen and two portions of liver. The stomach was complete. There was a small portion of duodenum attached to one end, which measured 2 cm. in length. The terminal end of the esophagus was also included. The proximal two thirds of the stomach on its anterior wall was injected, and occasional small fibrous adhesions were attached to it. The distal third was lined with rather smooth pale yellow serosa. There were two openings in the anterior surface of the stomach along the greater curvature. The more proximal one, which was located 3 cm. from the esophageal opening, measured 2.5 by 1 cm. The more distal one, which was located 6 cm. beyond the first, measured 3.5 cm. in diameter. However, the edges of these two openings could easily be brought together. The larger one had a portion of the liver attached to the pedicle. The piece of liver measured 5 by 2.5 by 1.5 cm. The liver was dark brown and friable and was attached rather intimately to the pedicle which covered the large opening. There was a moderate amount of gastrohepatic ligament attached. Within the gastrohepatic ligament just beneath the esophagus were several moderately firm grayish white lymph nodes varying from 0.5 to 1 cm. in diameter. They extended down for a distance of 3 cm. from the esophageal opening. Several cotton sutures were also noted on the gastrohepatic opening. The omentum attached to the greater curvature of the stomach varied in length from 1 to 2 cm. There were fibrous adhesions attached to it. In general the omentum was firm and coiled up on itself. Along the distal third of the greater curvature there were approximately six other lymph nodes varying from 0.5 to 1 cm. in diameter. These were pinkish gray, and the largest one showed an area which appeared to be well demarcated from the surrounding lymphoid tissue and measured 4 mm. in diameter. The mucous membrane throughout its entire length was injected and showed large areas of hemorrhage within the mucosa, especially in the midportion. In the fundal portion there was considerable ulceration, which extended in irregular fashion throughout approximately two thirds of the stomach and entered the body of the stomach. The intervening mucosa was polypoid in appearance. Some of the polypoid structures had flat tops. Others were dark red and elevated and varied from 1 cm. to 2 cm. in diameter. The wall of the stomach was moderately thickened, especially in the proximal two thirds. There was a certain amount of induration in this portion of the stomach. The distal portion was soft and pliable. There was another portion of the liver present, which was free and measured 6.5 by 2.5 by 1 cm. It was friable and reddish brown. The spleen measured 10.5 by 3.5 cm. The capsule was smooth except in the region of the pedicle, where there were three lacerations extending outward for a distance varying from 1.5 to 2 cm. and involving the capsule. On section the spleen was moderately firm. The splenic capsules were prominent. There was no invasion of fibrous tissue. The pulp was reddish brown.

The microscopic diagnosis was lymphosarcoma of the stomach, reticulum cell type, with metastasis to lymph nodes of the greater curvature.

SUMMARY

The subject of gastric sarcoma in general is briefly reviewed, and the incidence, clinical picture, pathology, prognosis and treatment are discussed. Ten previously unreported cases from the records of the Charity Hospital of Louisiana at New Orleans are presented.

215 Camden Street, San Antonio, Texas.

TREATMENT OF ACUTE CHOLECYSTITIS

A SUGGESTED TWO STAGE TREATMENT

DEAN MACDONALD, M.D.
ST. CATHARINES, ONTARIO, CANADA

The controversy over the treatment of acute cholecystitis seems to have produced no definite agreement. This is partly because the conclusions and deductions of the many analytic studies are based on variable and inconstant factors. This paper is an attempt to find a common denominator for these factors and to place the problem, from both the etiologic and the therapeutic viewpoint, on a more solid pathologic basis. Such a state is desirable in view of the increasing consciousness that serious complications are more common than was formerly believed (empyema of the gallbladder, pericholecystitis, fistula formation, gangrene, perforation and such conditions).

The prevailing discussions do not, nor does this one, concern the general treatment, on which all physicians agree—namely, that the patient must be carried over the immediate dangers with the greatest assurance of safety. Rather, they concern the method by which this should be accomplished—i. e. medical therapy, which is conservative, or surgical therapy, which may be either radical or conservative. The majority will agree that in many instances a major curative surgical procedure can be carried out with more safety, less technical difficulty and less shock-precipitating trauma after the acute manifestations have receded (e. g. edema, congestion, localized necrosis, vascular thrombosis, lymphangitis, infection, hepatitis and suppuration)—if these conditions do recede, and if the resulting pericholecystic pathologic changes do not predispose to too much trauma when operation is done, and if the patient does not die as a result of the acute attack.

The possibility of a happy medium, a combination of the forms of therapy, seems to have been forgotten. This is due to several factors, the recognition of which will make one consider this condition with more deliberation. These factors are, principally: (1) failure to recognize acute cholecystitis as the consequence of an acute obstruction in an abdominal tube the distal end of which is closed (other causes of obstruction are recognized, but they are, for practical purposes, uncommon); (2) failure to recognize it as a progressive disease in itself as well as a most important step in the progression of chronic cholecystitis and its complications (i. e., progressive if an active effort is not made to prevent it); (3) failure to classify it as early or late according to the age of the pathologic changes rather than the age of the symptoms; (4) failure to consider the age of the patient. The older the patient, the greater is the likelihood that extracystic disease is present and that cardiovascular and renal disease may precipitate serious complications. Hence the physical status of the patient determines, in some degree at least, the treatment.

Acute cholecystitis is a symptom of an acute obstruction of the cystic duct. This is the fundamental pathologic condition.[1] Acute cholecystitis is, therefore, an end result, and its occurrence in a patient in or past the forties is presumptive

1. Macdonald, D.: The Postural Treatment of Biliary Colic: Its Relationship to Acute Cholecystitis, Am. J. Digest. Dis. **10**:138 (April) 1943.

evidence that extensive disease probably exists throughout the biliary system as well as in the gallbladder proper. Curative treatment will, consequently, be more than just the usual correction of an obstruction and possibly the removal of the nonviable part; it must also concern the associated and complicating condition (which involve the pancreas, liver, common duct and other organs). Hence the decision regarding the type and the timing of such treatment cannot always be based on statistics compiled after studying the records of patients operated on, or not operated on, so many hours after such and such an occurrence. This statement is further supported by the following facts: (*a*) Just as in all disease processes there is no definite or reliable correlation between the onset of the original pathologic changes and the first appearance of clinical complaints, so there is none in acute cholecystopathy. Pathologic changes may progress while the clinical symptoms and signs regress. In other words, the gravity of the clinical picture is never a reliable guide to the seriousness of the disease process. Hence such a word as "early," "late," "deferred" or "immediate" as a qualifying adjective for "operation" has little meaning from a pathologic viewpoint. (*b*) In such statistics "operation" means only that surgical intervention has been performed, and it does not always refer to any particular type, although cholecystectomy predominates. (*c*) Reference is rarely made to the anesthetic agent or to the anesthetist, and both these factors have more than a little influence on the outcome of any operation, whether it is a tonsillectomy or a total gastrectomy. (*d*) The threshold for pain and the constitutional stability of the patient are among the most inconsistent and variable factors in medicine, and these factors cannot be evaluated in large groups of patients. Therefore, in disease of the gallbladder of recent and acute onset, statistics should never completely influence the decision regarding therapy, because a decision can be made only on the case at hand, and the best decision can be made only if the actual and potential pathologic pictures are thoroughly understood and clearly visualized in relationship to the physical status of the patient. The latter point is the foundation on which the decision must be based, whether medical or surgical treatment is indicated. Patients cannot always be classified as surgical or medical on such variable bases as the number of hours they have felt sick and the number of hours they have been confined to a hospital bed. At any rate, such bases cannot be taken as standards. There must be a more constant criterion on which to base treatment. This is the cause producing the pathologic state, which is, as previously mentioned, an obstruction in an abdominal tube. Acute cholecystitis is merely a symptom of this underlying cause. It seems that this is the most commonly overlooked factor in the clinical evaluation of acute inflammation of the gallbladder.

Statistics show that a high mortality rate follows late drainage. This is true, but it is not fair to the surgical procedure of cholecystostomy, because it is so often chosen for patients who are too sick to withstand anything more serious and who would probably have died under any circumstances. Patients do not die as the result of drainage of the gallbladder; they die because it is deferred too long. These are procrastination deaths; they are not operative deaths. The very fact that cholecystostomy is the procedure of choice for the sickest patients indicates that drainage per se is the least serious and dangerous of all biliary operations. In this regard, the status of cholecystostomy is comparable to that of cesarian section of a few years ago in that they were both regarded more or less as "last resorts." The lowering of the mortality rate of cesarian section is undoubtedly due to early and preventive surgical intervention. If drainage of the gallbladder is used as a preventive procedure rather than as "the only thing to do because

the patient cannot stand anything else," it will lose its black name, and it will become an important factor in treatment too. Hence a brief and general discussion of the advantages of a two stage operation in certain cases of acute cholecystitis is presented. The first stage (drainage) is preventive for the immediately dangerous phase; the second stage is curative for cholecystopathy and the associated conditions.

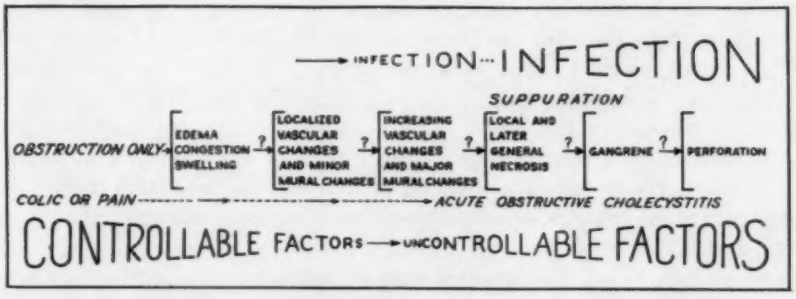
It would seem that a two stage operation answers many of the arguments of both the proponents and the opponents of immediate cholecystectomy. This procedure has greatly improved the surgical end results for other conditions, for example, certain types of perforative appendicitis, and for operations such as prostatectomy and many types of intestinal resection. It should therefore at least deserve serious consideration in this situation before being discarded, or even before being accepted. It is hoped that this presentation will stimulate such a discussion, which, however, cannot be thorough unless it is recognized that conservative (passive or medical) treatment does not control the factors which determine whether an acute obstruction of the cystic duct will resolve or progress to perforation. In conservative treatment the physician watches the course of acute obstructive cholecystitis but he does not change it. If it changes, it is changed by factors out of his control; that is, it resolves because of good luck and not because of good management, as witness the many instances in which it has occurred and subsided without the appearance of clinical signs or symptoms.

The suggestion is made, based on only 12 studied cases [2] and a thorough review of the literature, that the first stage, which is preventive and must be early, should consist of a simple and quick drainage of the bladder by use of a small mushroom catheter and when indicated a local anesthetic. This prevents the progression of pathologic changes to the dangerous phase and allows the physiologic functions to return to normal before extensive surgical procedures are performed. It obviates, moreover, what some authors refer to as the life-saving measures which should be resorted to before the so-called delayed operation is done, a warning which, in itself, means that the patient must present a bad risk for surgical intervention. Drainage allows the pressure inside the bladder to be reduced below the perforating point, if not to zero, in addition to preventing the immediately serious and potentially fatal complications. Drainage also predisposes to a quicker and more sure convalescence and reduces the incidence of pericholecystitis, of fistula formation and of other conditions, which make trauma a major factor in later surgical treatment. At the time of drainage an effort must, of course, be made to remove calculi from the cystic duct. This will consist in treating prophylactically and somewhat curatively the entire ductal system, particularly the common duct, by free drainage through the cystic duct, provided edema, swelling and congestion have not completely obstructed the latter; if such inflammatory obstruction is present, the removal of the mechanical obstruction and/or the release of the intravesical pressure would promote resolution in the area of the cystic duct and allow drainage from the great ducts. If drainage is performed early, few adhesions will be broken; local peritonitis will not likely be extended; the immediate dangers will, for practical purposes, be abolished, and cholecystectomy plus the often necessary operation on the ducts, which constitutes the second stage, will be done in a patient who presents a better risk owing to the absence of an acute pathologic condition and unbalanced physiologic processes. Thus the immediate and dangerous phase is passed over with a minimum of danger as interpreted by the

2. Seven personally observed cases and 5 studied by permission of Drs. A. H. Greenwood, A. M. Anderson, J. S. Sheahan, A. D. Konkin and W. D. Cornwall.

internist as well as by both the radical and the conservative surgeon. This procedure is physiologically and pathologically sound. It is also conservative therapy, and it is based on the often proved and well recognized surgical axiom that the progression or regression of any pathologic process which is the result of complete obstruction of a tube depends directly and indirectly on the release of that obstruction. This principle applies to any hollow viscus, whether it is the cystic duct, the small bowel (strangulated hernia) or a blood vessel (embolism). Rational treatment for any patient with abdominal obstruction is the release of that obstruction. And yet the physician often "sits by the patient" with acute obstruction of the cystic duct! This is often physiologically and pathologically unsound, no matter how favorable the results of a "watching and waiting" regimen may seem. Conservative medical treatment is not successful just because the patient does not die.

There is general agreement that the therapy of chronic calculosis should never be expectant; and both the immediate and the future dangers of acute diseases are greater.[3] It therefore follows that the treatment of acute disease should, theoretically, never be expectant. When a patient first complains of symptoms of obstruction of the bowel one does not wait for signs or symptoms to appear which prove that the obstruction is complete and progressing; one prevents as much "trouble" as possible by using surgical intervention judiciously and prophylactically. This is the spirit in which cholecystostomy should be employed.



This represents, in a schematic way, the principal steps in the possible progress of acute cholecystitis when it is treated conservatively. Early in its course, when the obstruction is uncomplicated, the controllable factors are maximal; as the calculus becomes locked in place and local changes occur, these controllable factors gradually decrease until when infection is added to the minor complications they completely disappear and become the uncontrollable factors, which increase in direct proportion to the progress of the infection. These uncontrollable factors include physiochemical imbalances, hepatic damage, infection and suppuration. Fortunately, these late complications are not too common (though they are not uncommon).

The second stage, which is the actual *curative* effort, allows cholecystectomy to be performed and the ductal system to be treated with much less risk, much less trauma and much more thoroughness. This two stage attack is of particular significance for the older age group.

There is also the added and obviously important advantage in the two stage operation of one's being able to view the intrahepatic and extrahepatic ductal system by cholangiography and to determine the location and size of calculi in the ducts, if any are there, before the second operation. Perfusion can also be performed in selected cases and may be of great value.[4]

3. One of these dangers concerns the sudden upset in the physiochemical balance of the liver, which in chronic disease has had an opportunity to become partially balanced. This is less likely to happen in acute cholecystitis, because there are two pathologic processes involved.

4. Macdonald, D., and Drysdale, H. R.: Surgical Treatment of Medical Jaundice, Am. J. Surg. **60**:122 (April) 1943.

Those who prefer conservative therapy and argue that surgical intervention is easier and safer after the subsidence of acute symptoms will probably agree that the two stage operation has much in its favor because the potential complications consequent on conservative treatment are reduced to a minimum, because the dangers and difficulties of later cholecystectomy are minimized and because thorough and curative surgical procedures, particularly on the ductal system, are better performed at a later date. It will probably find less favor with those who believe in early radical operation.

A NOTE REGARDING OBSTRUCTIVE JAUNDICE

In selected cases a two stage operation for the relief of inflammatory obstructive jaundice, which is one of the most potentially serious of the common conditions with which the surgeon has to deal, has some of the advantages just mentioned, but there are added ones. (This obviously does not apply to obstructive lesions in the hepatic ducts.) This procedure is also of value if jaundice is the result of acute hepatitis consequent on acute cholecystitis. (By the two stage method the curative procedures, which are usually necessary and which are often technically difficult, are not performed on a patient who represents a bad risk.) Certain it is that cholecystostomy, performed with a local anesthetic, will not produce the morbidity or the mortality that results from extensive surgical interventions on jaundiced patients, because the physicochemical upset consequent on obstructive jaundice is great. The patient is also spared submission to anesthesia in his serious condition. It is recognized, of course, that the dangers are usually reduced if the bilirubin content of the blood is allowed to become stationary or preferably to return to normal, but during this stage of waiting the liver is continually being damaged, particularly if the time elapsed is long. The two stage attack will also permit the many advantages of cholangiography to be made use of.

COMMENT AND SUMMARY

The present criteria for determining the type and the timing of the treatment of acute cholecystitis do not seem to be pathologically sound. For instance, the time element is too variable; the type of operation is not constant; the influence of anesthesia is rarely mentioned; the individual constitutional stability of patients cannot be evaluated in large groups, and the condition is often considered as a disease entity whereas it is really a symptom and a sign of a serious abdominal condition, namely, an acute obstruction. The potential seriousness of all obstructive lesions is well recognized; they demand active and early treatment. There is also failure to consider this condition as positive evidence of progressing pathologic change of the biliary system and to remember that the clinical picture is not always correlated to the active pathologic process.

A two stage surgical procedure is suggested as a new method of treatment in certain cases, particularly when the lesion is in an early stage, and is based on the etiologic factors and the resultant pathologic state. The first stage consists of cholecystostomy, which is preventive, and the second stage of cholecystectomy plus a ductal operation, which is curative.

The two stage operation has lowered the mortality of many surgical conditions and operations, for example, of some types of perforative appendicitis and of many types of resection of the bowel. It is suggested that the same basic principles deserve serious consideration in connection with certain types of biliary disease.

Some advantages of a two stage operation for patients suffering with obstructive (inflammatory) jaundice are also mentioned.

The theoretic and practical advantages of the two stage procedure are summarized as follows and are presented with the hope that they will stimulate a thorough discussion and evaluation of this important subject.

(1) In cases of acute cholecystitis:

(*a*) That it prevents the serious or the potentially fatal complications resultant on conservative treatment.

(*b*) That it averts pericholecystic pathologic changes (e. g. fistula formation) which make trauma a serious factor at later operations and, indeed, may make curative surgery possible only in the hands of the most experienced.

(*c*) That cholangiography may often be of great help before the second stage.

(*d*) That cholecystectomy and surgical treatment of the common duct (which is so often a part of successful surgical treatment of the gallbladder) can be performed with much more thoroughness and safety in a quiescent stage than during the acute active phase.

(*e*) That it obviates dangers related to removal during the acute stage, not the least of which is a traumatic stricture of the common duct.

(*f*) That it predisposes to the return of a normal physiochemical balance and a general improvement in the physical status before extensive surgical intervention is done.

(2) In cases of obstructive jaundice:

(*a*) That the serious and always potentially dangerous surgical work is performed on a patient who presents a much safer risk at the second stage, in the absence of jaundice and in the presence of improved biliary and hepatic function.

(*b*) That cholangiography may be a definite help in the second stage, in that the presence and location of ductal stones can be determined.

(*c*) That perfusion will have helped to improve the blood and lymph circulation and to remove infection throughout the biliary system.

(*d*) That the decompression of the liver is much more gradual and less dangerous when carried out slowly through the gallbladder.

(*e*) That the morale of the patient is improved tremendously after the first stage, when the jaundice is reduced and the symptoms subside. This cannot be stressed too much.

12 King Street.

INFLUENCE OF HEPATIC FUNCTION ON METABOLISM OF VITAMIN A

KARL A. MEYER, M.D.

FREDERICK STEIGMANN, M.D.

HANS POPPER, M.D.

AND

WILLIAM H. WALTERS, M.D.

CHICAGO

Many facts indicate an influence of the liver on the metabolism of vitamin A. In acute [1] and chronic [2] hepatic disease the vitamin A content of the blood is low. Night blindness due to deficiency of vitamin A has been reported in acute hepatitis [3] and in cirrhosis even without jaundice.[4] The vitamin A content of the liver is low in chronic hepatitides (cirrhoses) [5] and variable in acute hepatitis and in catarrhal or arsphenamine jaundice.[6] The histologic distribution of vitamin A in the liver is considerably changed by damage to the liver.[7] Several factors have been mentioned to explain the foregoing observations, such as: (1) faulty absorption of vitamin A and especially of carotene from the intestinal tract [8]; (2) inability of the liver to store vitamin A, although more emphasis is laid on alterations of the reticuloendothelial system than on damage to the hepatic parenchyma [9]; (3) inability of the liver to convert carotene into vitamin A [10]; (4) an increased demand for vitamin A in hepatic disease.[11] However, the mechanism of this disturbance is still not clear. Knowledge of the mechanism of the disturbance of the metabolism of vitamin A in hepatic disease is necessary for its correction.

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From the Cook County Hospital, the Department of Surgery, Northwestern University, and the Department of Internal Medicine and Pathology, University of Illinois College of Medicine, and the Cook County Graduate School of Medicine.

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Studies of biopsy specimens from the liver [12] were undertaken to compare the level of vitamin A in the blood before and after feeding of large doses of vitamin A with the hepatic content of vitamin A and with its distribution as seen by fluorescence microscopy. In addition, routine and fluorescence microscopic study of a great number of biopsy specimens from the liver provided an opportunity to investigate the incidence of anatomic changes in the liver in the diseases studied, especially since the normal morphologic pattern of the vitamin A fluorescence is disturbed before alterations are seen on routine histologic examination.[13] From these studies information was obtained which, with the established knowledge, may clarify the relation between impairment of hepatic function and metabolism of vitamin A and at the same time give the indications for vitamin A therapy in hepatic disease.

MATERIAL AND METHOD

In 75 cases, biopsy specimens were taken at operations for various diseases affecting the upper part of the abdomen. The vitamin A content of the plasma was determined during operation. In most of the cases, several determinations of plasma vitamin A were made prior to the operation. In some of them the variation of the level following the administration of 75,000 U. S. P. units of vitamin A [14] was observed (discussed in a previous paper [15]), and in 7 cases the influence of daily feeding of 500,000 U. S. P. units of vitamin A for three to six days was studied. These procedures are responsible for the occasional differences between the plasma vitamin A level during operation which was used for comparison with the hepatic level (described in a previous publication [12b]) and the preliminary vitamin A level which is reported in the tables to follow. Since in the cases in which 500,000 U. S. P. units of vitamin A was given the hepatic vitamin A concentration was influenced by the huge doses, the hepatic values in the tables are marked by an asterisk but omitted from table 7. For completeness, the blood levels obtained in cases of cirrhosis and hepatitis are included in table 7 to provide comparative data on patients most of whom did not come to operation. In all cases some of the following clinical tests of hepatic function were performed prior to operation:

1. Determination of nitrogen, total protein, albumin and globulin of the plasma.[16]
2. Determination of plasma prothrombin concentration (Quick's method).[17]
3. Determination of icterus index.
4. Determination of blood cholesterol and cholesterol esters.[18]
5. Determination of alkaline serum phosphatase.[19]
6. Oral hippuric acid test.[20]
7. Oral galactose tolerance test.[21]
8. Cephalin-cholesterol flocculation test.[22]
9. Quantitative determination of excretion of urobilinogen in the urine and feces.[23]

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The vitamin A was determined in the plasma and the liver, partly according to Josephs' method [24] and partly according to Kimble's,[25] with the photoelectric colorimeter. The values obtained by both methods, which were slightly modified, checked. The methods used were described in detail in a previous publication.[12b] The part of the liver specimen which was used for histologic examination was fixed in solution of formaldehyde U. S. P. (diluted 1:10). After two hours frozen sections were made. Some of these were examined under the fluorescence microscope for vitamin A fluorescence and fat.[26] Other sections stained with sudan III were examined in visible light. The rest of the specimen was embedded in paraffin and sections stained according to routine methods.

The vitamin A distribution under the fluorescence microscope in necropsy and biopsy specimens from subjects with various pathologic conditions has previously been described.[27] In the normal liver vitamin A fluorescence may be imparted to the Kupffer cells by lipid droplets, to the epithelial cells by small lipid droplets at their edge, by mitochondria, by lipofuscin, by a few scattered large fat droplets and by the cytoplasm, which has a rather dull, diffuse fluorescence. The normal pattern of the vitamin A fluorescence is easily disturbed. Hence minor alterations were found in nearly all specimens of liver obtained for biopsy or necropsy. In definite pathologic conditions these alterations were extremely evident. One or more of the following alterations of the uniform fluorescence picture may occur. Irregular distribution of vitamin A fluorescence may be seen without change in the morphologic appearance in visible light. This irregularity may or may not be related to the topography of the lobule. Sometimes irregular foci are found with fluorescence obviously different from that of the surrounding tissue. In some areas only the Kupffer cells, and in others only the liver cells, show fluorescence, and in still others, neither shows it. The fine lipid droplets may be missing or irregularly distributed throughout the cell or be free of vitamin A fluorescence. Larger fat droplets of various sizes and in various numbers may be present with diminished, variable or no fluorescence. The tables which follow record the total amount of vitamin A fluorescence and the degree of alteration. The latter may be considered as a visual manifestation of disturbed vitamin A metabolism and also as a morphologic index of impairment of hepatic function.

To simplify the tabulation of the routine histologic examination the following symbols (numerals and letters) are used in describing the changes of the hepatic parenchyma and of the periportal triads respectively.

Hepatic Parenchyma.

1. Irregularity in the size of the cells and of the nuclei, usually combined with irregular mitosis.

2. Separation of the Kupffer cells from the hepatic cell cords. This mobilization is usually combined with proliferation of the Kupffer cells and widening of the tissue spaces between the hepatic cell cords and the blood sinusoids. The toxic edema or serous hepatitis [28] is usually localized. Its significance is questionable.[29]

3. Accumulation of large fat droplets recognizable in visible light.

4. Leukocytic infiltration in the interstitial spaces (usually localized).

5. Scattered small foci of necrosis characterized by breaking up of the hepatic cell cords, lack of nuclear staining and leukocytic infiltration.

6. Central necrosis, often seen in jaundice and associated with imbibition of bile pigment. The areas of necrosis may show all stages from simple lack of nuclear staining, with imbibition of bile pigment, to disappearance of the hepatic cells in a wide central area with collapse of the framework, proliferation of the connective tissue and dilatation of the sinusoids.

7. Interstitial hepatitis, characterized by intralobular connective tissue proliferation, leukocytic infiltration, and necrobiosis with regeneration of the epithelial hepatic cells.

The changes represented by the numerals 5, 6 and 7 were considered definite evidence of parenchymal damage.

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A. Lymphocytic infiltration of the periportal field varying from a few scattered lymphocytes (seen in practically all cases) to dense infiltrations which nearly simulate lymph follicles.

B. Leukocytic infiltration of the periportal field mostly associated with cholangiolitis.

C. Enlargement of the periportal field due to proliferation of connective tissue (fibrosis).

D. Proliferation of the small bile ducts.

RESULTS

The patients examined are grouped according to their disease.

Peptic Ulcer.—Of 22 patients with gastric or duodenal ulcers, none showed signs of impaired hepatic function, except that 3 patients with bleeding ulcers had pathologic cephalin-cholesterol flocculation. Two livers showed fatty changes. In only 1 liver were there definite pathologic changes in the parenchyma. Lymphocytic infiltration and fibrosis were common in the periportal fields of all livers. The disturbance of the vitamin A fluorescence pattern was notable in only 1 case. The total amount of fluorescence was normal (fig. 1). The hepatic vitamin A concentration was also relatively high, and the blood vitamin A levels were with a few exceptions within normal limits. No great discrepancy between the level of vitamin A in the blood and in the liver was encountered (table 1).

Carcinoma of the Stomach.—In this group there were 7 patients with carcinoma and 1 with tuberculosis of the stomach. Three showed clinical signs of impairment of liver function, but in only 1 of them (the tuberculous patient) were definite pathologic changes present in the liver. Much vitamin A fluorescence with only moderately disturbed distribution was seen. Only the 4 patients not receiving large doses of vitamin A were representative for this study, but even these showed rather high amounts of hepatic vitamin A, which contrasted often with a low level of vitamin A in the blood (table 2).

Disease of the Gallbladder Without Jaundice.—In this group of 17 patients only 2 had questionable clinical evidence of damage to the liver. On histologic examination 1 showed miliary necroses and fatty changes and 4 had fatty changes only. The alterations in the periportal fields were much more developed than in the previous groups. The disturbance of the vitamin A fluorescence was not more evident than in the other groups. One phenomenon, however, was rather common, namely the frequent appearance of fat droplets without vitamin A fluorescence (fig. 2). Chemically and histologically the total amount of vitamin A in the liver was within normal limits. The blood levels were also fairly normal (table 3).

Disease of the Gallbladder with Jaundice.—This group included 13 patients with various degrees of icterus. Of the 11 patients examined, 4 showed definite, 4 questionable and 3 no clinical evidence of impairment of hepatic function. Morphologic evidence of damage to hepatic cells did not parallel the results of clinical tests of hepatic function. Signs of damage to hepatic cells were found in 6 cases, the incidence being fairly parallel to the duration of the jaundice. In none had the jaundice existed less than four weeks, while in those without damage to the liver the icterus was never of more than five weeks' duration. Pathologic changes in the periportal field were common. The vitamin A fluorescence showed great variation in its total amount, and, especially in the patients with evidence of hepatic damage, the vitamin A fluorescence pattern was greatly disturbed (figs. 3 and 4). Even if the patients to whom large amounts of vitamin A were administered were omitted, the total amount of vitamin A in the liver varied between 7 and 140 micrograms per gram of liver. The plasma vitamin A also showed great variation and was especially low in most of the patients with pathologic changes (table 4).

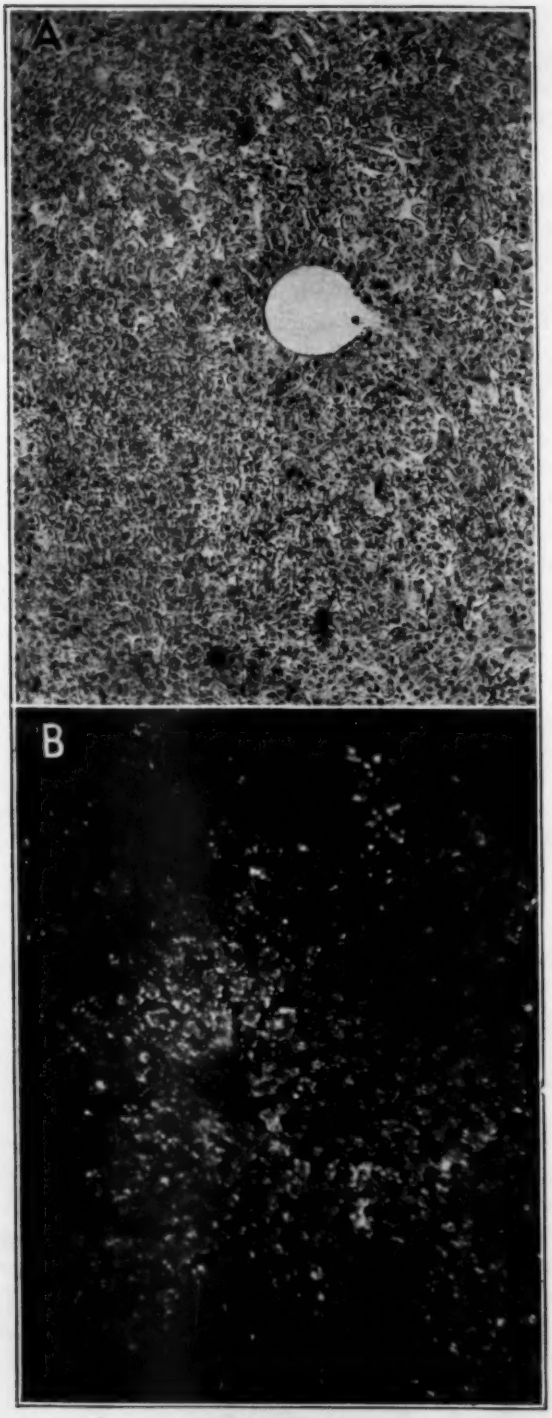

Fig. 1.—Photomicrographs of a biopsy specimen from the liver of a patient with peptic ulcer without damage to the liver. *A*, routine histologic examination: normal structure of the hepatic parenchyma. *B*, examination with fluorescence microscope: vitamin A fluorescence imparted by fine lipid droplets at the edge of the liver cells and in the Kupffer cells.

TABLE 1.—*Patients with Peptic Ulcer*

Initials	Sex and Age	Site of Ulcer	Clinical Evidence of Damage to Liver	Routine Histologic Evidence of Damage to Liver: Parenchyma	Routine Histologic Evidence of Damage to Liver: Periportal Field	Fluorescence-Microscopic Observations: Total Vitamin A Fluorescence	Fluorescence-Microscopic Observations: Degree of Disturbance of Distribution	Vitamin A in Micrograms per: Gm. of Liver	Vitamin A in Micrograms per: 100 Cc of Plasma
J. M.	F 54	Gastric	—	0	A	++	+	298	44
C. S.	M 63	Duodenal	—	3	A, C	+++	++	124	28
A. K.	M 32	Duodenal	—	0	0	+	±	70	44
S. S.	M 49	Duodenal	—	0	A	+	+++	29	35
F. D.	M 36	Duodenal	—	0	C	+++	+	19	35
L. I.	M 56	Duodenal	—	0	A	+++	+	113	53
W. N.	M 50	Gastric	—	0	A	+++	+	49	35
W. M.	M 34	Duodenal	—	0	A	++	++	108	100
J. K.	M 45	Duodenal	—	0	C	++++	+	270	59
F. D.	M 66	Gastric	—	0	A	+ - ++	++	52	16
W. W.	M 42	Duodenal	—	4, 5	A	+ - ++	++	63	27
R. M.	M 29	Duodenal	0	0	A	++	+	25	33
P. S.	M 59	Duodenal	—	0	A	+	++	24	22
A. M.	M 67	Duodenal	—	1, 4	0	++	+	99	38
Z. K.	M 23	Duodenal	—	2	A	+++	++	167	22
J. N.	M 38	Duodenal	0	0	A	+	++	47	43
J. Z.	M 54	Duodenol	—	3	0	++	±	92	11
F. J.	M 52	Duodenal	—	3	A, C	++ - +++	++	98	33
F. T.	M 29	Gastric	—	0	A	+ - ++	+	56	11
E. S.	M 41	Gastric	?	1	A	+	++	35	27
W. D.	M 34	Duodenal	?	1	A	+	++	93	22
R. G.	M 56	Duodenal	?	0	A	+	+	65	33
A. L.	M 40	Duodenal	?	1	A	+	+++	37	11

TABLE 2.—*Patients with Carcinoma of the Stomach*

Initials	Sex and Age	Diagnosis	Clinical Evidence of Damage to Liver	Routine Histologic Evidence of Damage to Liver: Parenchyma	Routine Histologic Evidence of Damage to Liver: Periportal Field	Fluorescence-Microscopic Observations: Total Vitamin A Fluorescence	Fluorescence-Microscopic Observations: Degree of Disturbance of Distribution	Vitamin A in Micrograms per: Gm. of Liver	Vitamin A in Micrograms per: 100 Cc of Plasma
J. S.*	M 57	Carcinoma of stomach	0	0	A	+++	±	123	10
J. H.*	M 33	Tuberculosis of stomach	?	2, 5	0	+++	++	307	24
L. O.*	M 28	Carcinoma of stomach	0	2	A	++++	++	435	17
G. B.*	M 56	Carcinoma of stomach	0	0	A	++++	+ - ++	548	44
N. C.	M 64	Carcinoma of stomach	0	0	A	+++	++	262	35
A. M.	F 69	Carcinoma of stomach	?	0	A	+++	+	429	22
J. P.	M 58	Carcinoma of stomach	?	2	A, D	+ - ++	++	31	11
H. G.	M 66	Carcinoma of stomach	0	2	0	+++	+	233	17

* Received several doses of 500,000 U. S. P. units of vitamin A.

Malignant Tumors with Jaundice.—In this group there were 10 patients, 1 of them examined twice, on occasion of two laparotomies. With the exception of 1 patient with only slight jaundice, all showed on clinical examination definite or questionable impairment of hepatic function and also showed pathologic changes in the hepatic parenchyma and the periportal fields. The total amount of vitamin A

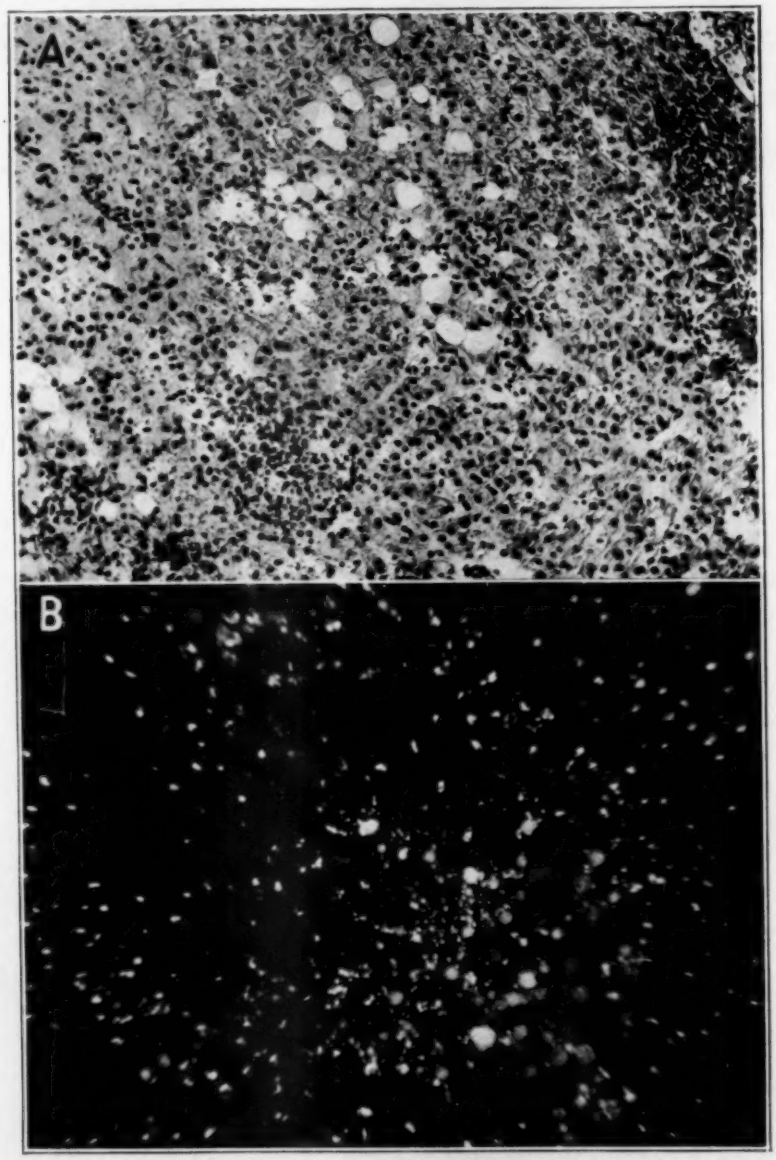

Fig. 2.—Photomicrographs of a biopsy specimen from the liver of a patient with gallbladder disease without jaundice. *A*, routine histologic examination: many large fat droplets scattered over the hepatic parenchyma. Extensive lymphocytic infiltration in the periportal field. *B*, examination with fluorescence microscope: the Kupffer cells impart a strong vitamin A fluorescence. In places, small lipid droplets in the hepatic cells impart a strong fluorescence. The large fat droplets have a varying, but usually low, fluorescence.

fluorescence was as a whole lower in this group than in the others. The disturbance of the vitamin A fluorescence pattern was considerable (fig. 5). The concentration

TABLE 3.—*Patients with Disease of the Gallbladder Without Jaundice*

Initials	Sex and Age	Clinical Evidence of Damage to Liver	Routine Histologic Evidence of Damage to Liver: Parenchyma	Routine Histologic Evidence of Damage to Liver: Periportal Field	Fluorescence-Microscopic Observations: Total Vitamin A Fluorescence	Fluorescence-Microscopic Observations: Degree of Disturbance of Distribution	Vitamin A in Micrograms per: Gm. of Liver	Vitamin A in Micrograms per: 100 Cc. of Plasma
M. K.	F 56	0	1	A, C	++	++	31	27
A. F.	F 62	?	1	A	+++	+	106	61
P. M.	F 51	0	0	0	++	±	49	35
T. H.	M 48	0	1	A, B	+	++	41	20
O. F.	F 65	0	0	A	++	+	59	52
Z. I.	F 37	0	0	A	±	+++	5	22
O. J.	F 41	0	0	C	+++	+	233	27
A. R.	F 29	—	0	A	++	+	41	33
L. M.	F 39	—	1, 4	A, C, D	+	++	35	27
L. B.	F 56	—	3	A	++++	+	217	38
A. P.	F 58	—	0	A	++	±	70	35
M. S.	F 52	—	3	A	++	+	74	66
U. L.	F 34	—	3	A	+ - ++	+	62	33
M. F.	F 53	?	3, 5	A, C	+ - ++	+	88	38
C. W.	F 46	0	3	A	++	++	20	33
L. B.	F 31	—	0	A, C	+ - ++	+	60	38
I. G.	F 36	—	3	A	+ - ++	++	41	27

TABLE 4.—*Patients with Disease of the Gallbladder with Jaundice*

Initials	Sex and Age	Icterus Index	Duration of Jaundice	Clinical Evidence of Damage to Liver	Routine Histologic Evidence of Damage to Liver: Parenchyma	Routine Histologic Evidence of Damage to Liver: Periportal Field	Fluorescence-Microscopic Observations: Total Vitamin A Fluorescence	Fluorescence-Microscopic Observations: Degree of Disturbance of Distribution	Vitamin A in Micrograms per: Gm. of Liver	Vitamin A in Micrograms per: 100 Cc. of Plasma
J. D.*	M 62	15	6 weeks	0	2, 4, 7	A	++++	+++	205	44
J. N.	F 46	43	1 year	+	1, 7	C	+	++++	80	3.5
F. T.	M 55	150	15 days	0	1	A	++	++	139	2
J. K.	M 33	37	10 weeks	+	Cholangitic abscesses		+	+++	50	0
R. B.	M 60	75	3 weeks	?	4, 6	A, B, D	±	++++	11	6
E. S.	F 44	53	8 weeks	0	5	A	++	+++	40	27
F. A.	M 52	111	4 weeks	?	1, 5	A, C, D	±	++++	7	4
M. M.	F 57	25	5 weeks	?	0	A, C	+++	++	140	17
I. H.	F 25	15	3 weeks	+	0	A	+++	++	122	33
A. M.	F 42	16	2 weeks	—	0	A	+ - ++	+	37	31
E. S.	F 31	46	1 week	—	3	a, c	++	++	15	38
M. B.*	F 60	24	3 weeks	?	1	A	++++	±	383	27
A. M.	F 22	58	2 weeks	+	0	A	++	+	81	22

* Received several doses of 500,000 U. S. P. units of vitamin A.

of vitamin A in the plasma and in the liver was relatively low, although the decrease in the plasma was often much more marked than that in the liver, producing evident discrepancies between the amount of vitamin A in the plasma and in the liver (table 5).

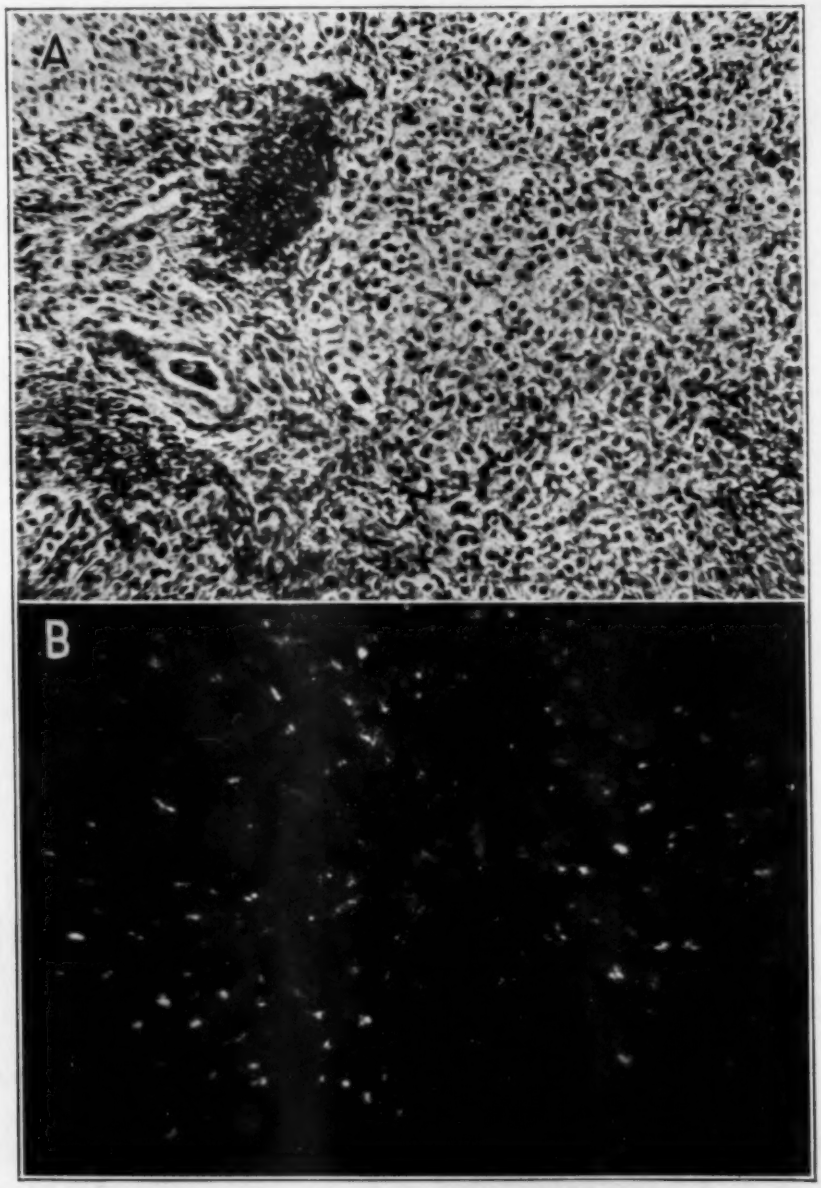

Fig. 3.—Photomicrographs of a biopsy specimen from the liver of a patient with disease of the gallbladder with jaundice of short duration and without clinical signs of damage to the liver. *A*, routine histologic examination: extensive lymphocytic infiltration in the enlarged periportal field. No visible damage to the parenchyma. *B*, examination with fluorescence microscope: irregular vitamin A fluorescence is imparted almost only by Kupffer cells. The bile casts in the enlarged bile capillaries appear black.

Cirrhosis.—Five patients with cirrhosis were examined. One had Wilson's disease (fig. 6); 1 had cirrhosis with primary carcinoma, and 3 had periportal

cirrhoses (fig. 7). The first 2 had no clinical evidence of damage to the liver, while the last 3 had such evidence and showed anatomic changes on histologic examination. In the latter 3 patients the plasma levels were zero, and in 2 of them

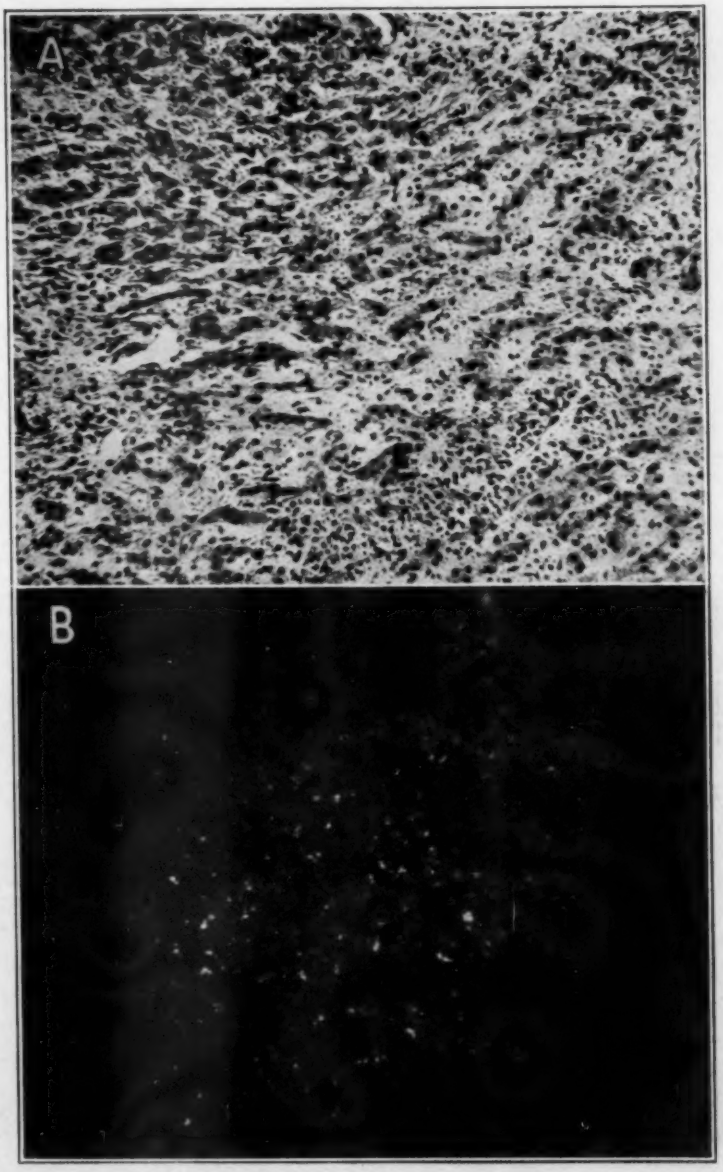

Fig. 4.—Photomicrographs of a biopsy specimen from the liver of a patient with disease of the gallbladder with jaundice of one year's duration and with clinical signs of hepatic damage. *A*, routine histologic examination: interstitial proliferation of connective tissue. Leukocytic and lymphocytic infiltration. *B*, examination with fluorescence microscope: small amounts of vitamin A fluorescence are seen in highly irregular distribution in Kupffer and hepatic cells.

the hepatic concentration was low. The distribution of the vitamin A fluorescence was much disturbed (table 6).

TABLE 5.—*Patients with Cancer of the Biliary Tract*

Initials	Age and Sex	Site of Lesion	Icterus Index	Duration of Jaundice	Clinical Evidence of Damage to Liver	Routine Histologic Evidence of Damage to Liver		Fluorescence-Microscopic Observations		Vitamin A in Micrograms per	
						Parenchyma	Periportal Field	Total Vitamin A Fluorescence	Degree of Disturbance of Distribution	Gm. of Liver	100 Cc. of Plasma
M. R.	M 52	Pancreas	333	2 weeks	+	2, 6	B, C, D	++	+++	110	0
A. D.	F 63	Stomach	103	3 weeks	+	1, 2, 6	A	+	+++	21	6
E. F.	M 44	Pancreas	156	8 months	+	6	A, B	+	+++	20	0
P. M.	M 29	Retroperitoneal sarcoma	150	5 months	+	6	A, B, C	—	—	40	22
M. B.	M 54	Pancreas	225	6 months	?	Biliary cholangitic cirrhosis		±	+++	5	5
W. M.*	M 60	Ampulla of Vater	56	5 weeks	+	1	A, B	++	+++	127	0
W. M.	M 60	Ampulla of Vater	50	7 weeks	+	1, 4	A, B	++	+	86	25
M. E.	F 67	Retroperitoneal tumor	8	?	0	0	A, C, D	++	+	187	17
D. S.	M 75	Pancreas	312	5 weeks	?	4, 6	A, B, C	± - —	+++	3.2	0
E. D.	F 60	Pancreas	71	8 weeks	+	1, 4, 5	A, C	+	++	55	6
M. K.	F 56	Pancreas	47	1 week	+	1, 6	A, C	+	+++	68	15

*Received several doses of 500,000 U. S. P. units of vitamin A.

TABLE 6.—*Patients with Cirrhosis of the Liver*

Initials	Sex and Age	Diagnosis	Icterus Index	Clinical Evidence of Damage to Liver	Routine Histologic Evidence of Damage to Liver		Fluorescence-Microscopic Observations		Vitamin A in Micrograms per	
					Parenchyma	Periportal Field	Total Vitamin A Fluorescence	Degree of Disturbance of Distribution	Gm. of Liver	100 Cc. of Plasma
I. H.	M 24	Wilson's disease	6	0	0	A, C, D	++	+	88	35
E. T.	M 60	Cirrhosis and carcinoma of liver	7	0	Tumor tissue		±	++++	11	8
F. G.	M 3?	Cirrhosis	10	+	Extensive decompensated cirrhosis		± - —	++++	0.2	0
J. M.	M 54	Cirrhosis	150	+	1	A, C, D	± - —	++++	3.5	0
H. B.	M 64	Cirrhosis	100	+	1 6	A, B, C, D	+	++++	74	0

TABULATION OF ALL THE FACTS OBTAINED

From table 7 it is evident that zero levels of vitamin A in the plasma were found in this series only in patients with far-advanced damage to the liver. All the patients with cirrhosis with jaundice and 66 per cent of those with primary or

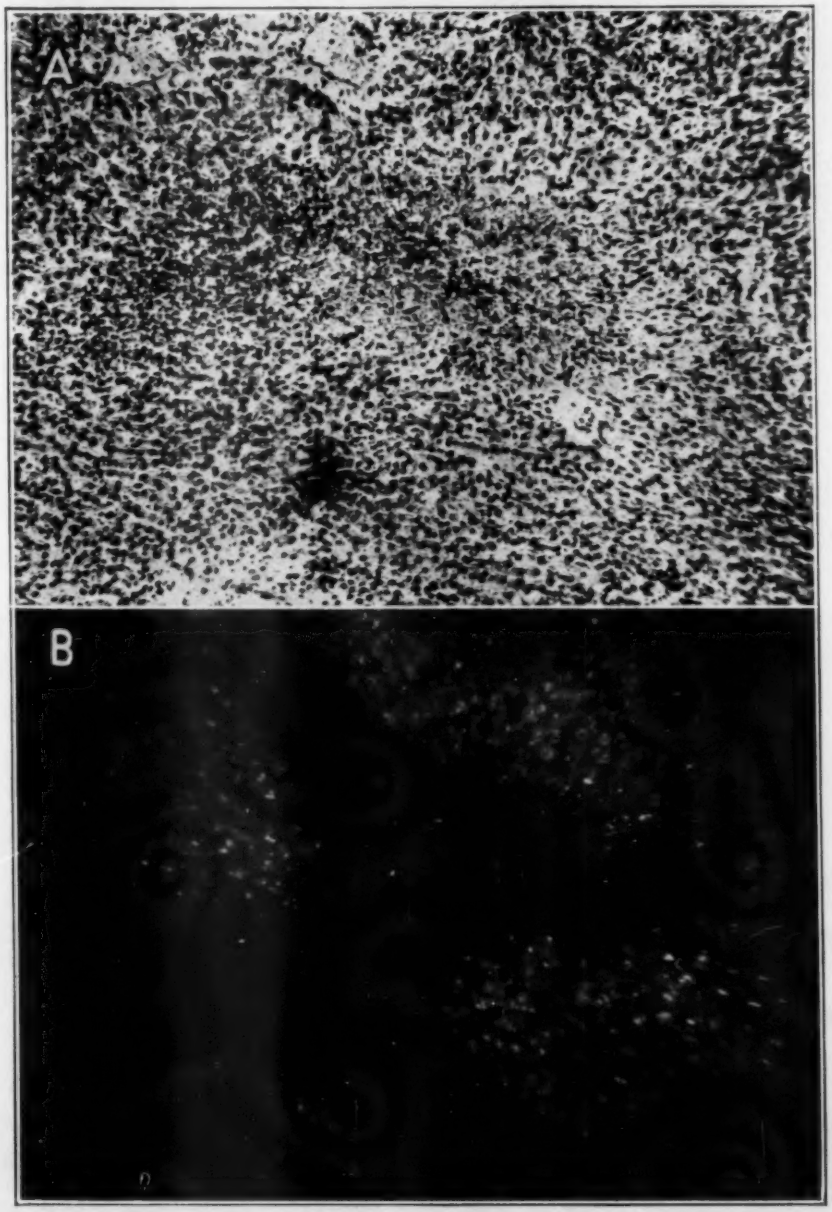

Fig. 5.—Photomicrographs of a biopsy specimen from the liver of a patient with jaundice due to malignant obstruction and with clinical signs of damage to the liver. *A*, routine histologic examination: central biliary necrosis with leukocytic infiltration. The surrounding hepatic parenchyma of the intermediary zone appears normal. *B*, examination with fluorescence microscope: the area of central biliary necrosis is free of vitamin A fluorescence. The bile casts appear as black spots. In the surrounding hepatic parenchyma irregular vitamin A fluorescence is imparted by the Kupffer cells and by some lipid droplets in the hepatic cells.

secondary hepatitis due to obstructive jaundice from carcinoma of the biliary tract had zero levels of vitamin A in the plasma. Some instances of a zero level were also found in patients with cirrhosis without jaundice or with secondary hepatitis from prolonged incomplete obstructive jaundice due to cholelithiasis. Paralleling

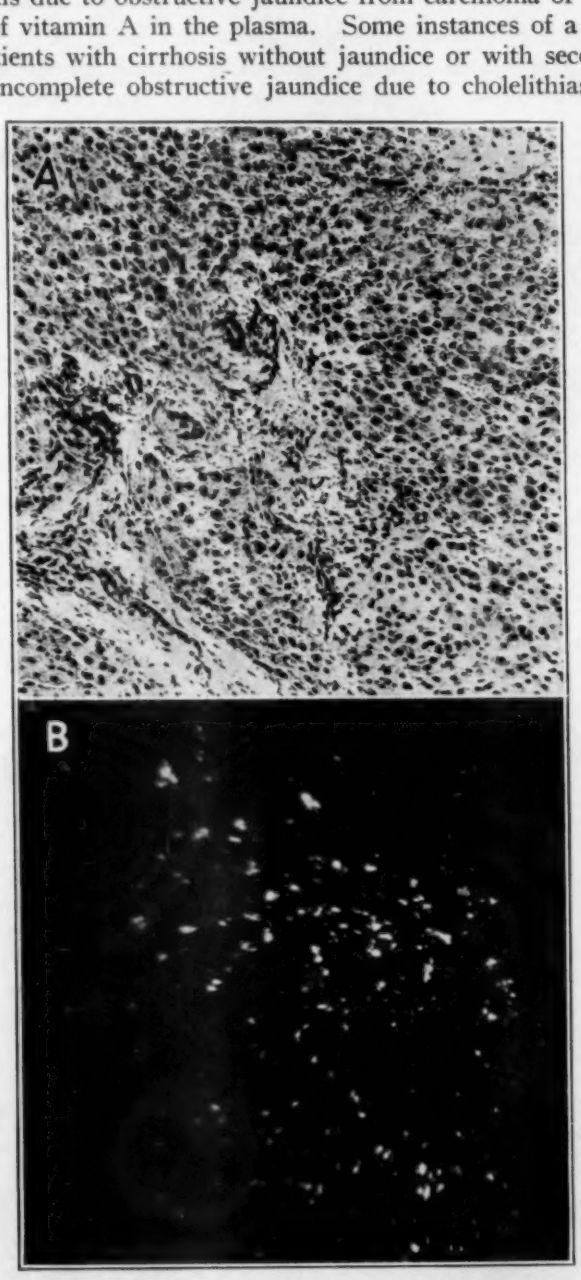

Fig. 6.—Photomicrographs of a biopsy specimen from the liver of a patient with compensated cirrhosis (Wilson's disease). *A*, routine histologic examination: enlargement of the periportal field due to fibrosis and lymphocytic infiltration. Proliferation in bile ducts—no signs of damage in the hepatic parenchyma. *B*, examination with fluorescence microscope: irregular distribution of the vitamin A fluorescence which is imparted by bizarre-shaped Kupffer cells and and irregularly distributed lipid droplets in the hepatic cells.

the incidence of zero levels the average of the plasma vitamin A levels in the aforementioned groups is very low. In benign or malignant obstruction there is a definite difference in the average of the plasma levels between the patients with

and those without hepatitis. Of the 3 patients in the other groups with morphologically apparent damage to the liver, only 1 had a low level of vitamin A in the plasma. The presence of extensive fatty changes, especially frequent in cholelithiasis, did not influence the levels of vitamin A in the plasma.

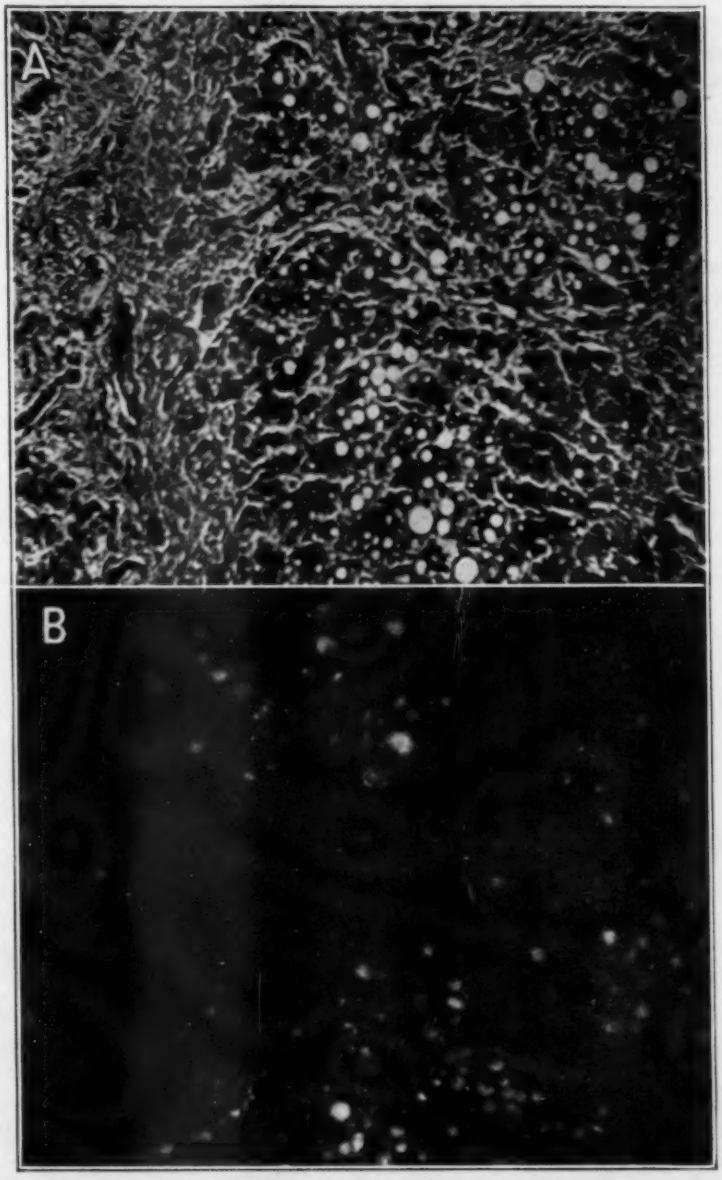

Fig. 7.—Photomicrographs of a biopsy specimen from the liver of a patient with cirrhosis with jaundice. *A*, routine histologic examination: extensive proliferation of connective tissue with lymphocytic infiltration and proliferation in the bile ducts. Many fat droplets of various sizes in the hepatic parenchyma. The cytoplasm of the hepatic cells is dark. *B*, examination with fluorescence microscope: vitamin A fluorescence imparted by a few irregularly shaped Kupffer cells and by the large fat droplets, the fluorescence of which is very low.

The average hepatic levels showed similar tendencies. They were low in the cases with damage to the liver and jaundice. Again, there is the characteristic

difference between cirrhosis with and without jaundice and benign and malignant obstruction with and without secondary hepatitis. Generally, the variations in the concentration of vitamin A were not as great in the liver as in the plasma, thus producing often a great discrepancy between a low content in the blood and a relatively high content in the liver. For comparison with the hepatic content of vitamin A the plasma obtained during operation was used. Its vitamin A level was often different from that of the first specimen, owing to preoperative administration of vitamin A. The discrepancy between the concentration in the liver and that in the plasma was especially evident in carcinoma of the stomach, although there was no morphologic evidence of damage to the liver. Absence of an increase in plasma vitamin A following administration of vitamin A was most common with damage to the liver.

COMMENT

The results of this study open two avenues of thought: (1) the relation of the disturbance of the liver to the metabolism of vitamin A and the therapeutic

TABLE 7.—*Summary of Data on Seventy-Seven Patients Subjected to Operation and Thirty Patients with Hepatic Disease Who Were Not Operated On*

Diagnosis	Total Number of Patients	Number of Patients with Plasma Vitamin A Level of Zero	Average Concentration of Vitamin A, in Micrograms per 100 Cc. of Plasma: Preliminary	Average Concentration of Vitamin A, in Micrograms per 100 Cc. of Plasma: During Operation	Average Concentration of Vitamin A in Micrograms per Gram of Liver
Cirrhosis without jaundice	10*	1	13	17	54
Cirrhosis with jaundice	16†	13	1	1.8	21
Hepatitis	9‡	5	3	—	—
Carcinoma of biliary passages with secondary hepatitis	10	6	7	8§	52§
Carcinoma of biliary passages without secondary hepatitis	1	0	17	17	187
Disease of gallbladder with jaundice and with hepatitis	6	1	14	11§	38§
Disease of gallbladder without hepatitis	7	0	24	31§	97§
Disease of gallbladder without jaundice and without hepatitis	11	0	34	35	67
Disease of gallbladder without jaundice and with hepatitis	1	0	39	39	88
Disease of gallbladder with fat in liver	5	0	39	39	83
Carcinoma of stomach without damage to liver	7	0	24	21‖	238‖
Tuberculosis of stomach with damage to liver	1	0	2.3	—§	—§
Peptic ulcer without damage to liver	22	0	35	33	92
Peptic ulcer with damage to liver	1	0	27	27	63

* Eight of these were not operated on.
† Thirteen of these were not operated on.
‡ None of these were operated on.
§ One patient left out because he received 500,000 U. S. P. units of vitamin A.
‖ Three patients left out because they received 500,000 U. S. P. units of vitamin A.

considerations derived from it, and (2) the utilization of chemical and of fluorescence-microscopic demonstration of vitamin A in ascertaining the presence and degree of damage to the liver.

Confirming previous reports, this study also reveals that with damage to the liver the level of vitamin A in the plasma is low. The lowest averages and the most zero levels (with the method used) are found in progressive cirrhosis with superimposed hepatitis and manifest jaundice. In cirrhosis without acute hepatitis as indicated by the absence of manifest jaundice the average plasma vitamin A level is slightly higher. Similarly, with obstructive jaundice the lowest levels are found in patients with superimposed hepatitis, in agreement with Stewart and Rourke.[30] In our cases the secondary hepatitis was more common in cancerous complete biliary obstruction than in benign incomplete obstruction. With uncomplicated obstructive jaundice the level of vitamin A in the plasma is almost normal.

In the absence of gross nutritional deficiency, a plasma vitamin A level of zero indicates severe damage to the liver whether jaundice is present or not or whether the hepatitis is primary or secondary to an obstructive phenomenon. In the 3

30. Stewart, J. D., and Rourke, G. M.: Surgery **11**:939, 1942.

patients without obvious hepatic disease or jaundice in whom the histologic examination revealed miliary necrosis of the hepatic parenchyma, the plasma level was low in only 1. However, the functional significance of the necrosis is questionable, as will be discussed later. A normal blood level of vitamin A does not necessarily exclude some damage to the liver; a zero or close to zero level is definite evidence of damage to the liver provided nutritional factors can be excluded. Lack of vitamin A in the blood may even be of diagnostic value comparable to that of the known drop of vitamin K activity in similar conditions. Confirming the observations of Abels and his associates [31] in cases of carcinoma of the stomach, somewhat low plasma vitamin A levels were found which were associated with normal hepatic stores of the vitamin and relatively high incidence of functional impairment of the liver. An explanation for this cannot be given at present.

To explain the low plasma level of vitamin A in hepatic disease and its significance from the point of view of vitamin A therapy, prior studies on the relation between plasma and liver vitamin A [12b] and the intestinal absorption of vitamin A can be referred to.[15] In patients with a low plasma level of vitamin A and damage to the liver, we found, as did others,[32] an impaired intestinal absorption of vitamin A; the blood level failed to rise on oral administration of 75,000 U. S. P. units of vitamin A. The nearest explanation for the disturbed absorption of vitamin A would be the jaundice, since lack of bile acids prevents the absorption of carotene [10] and possibly interferes with that of the fat-soluble vitamin A. The impairment of absorption, however, does not run parallel to the degree and type of jaundice—hepatic or obstructive. Low blood levels of the vitamin are also found in cirrhosis without jaundice. Hence the hepatic damage itself is probably responsible. However, impaired absorption is not the only factor causing a lack of vitamin A in the plasma. In acute hepatitis the impairment of absorption does not exist long enough to deplete the blood if the stores in the body are sufficient. A diet completely free of vitamin A fails for a long time to reduce the plasma vitamin A in normal adults.[33] The relation between the vitamin A content of the liver (which contains 95 per cent of the vitamin A in the body [34]) and that of the plasma is significant. If, as seen under the fluorescence microscope, the distribution of vitamin A in the liver becomes too much altered, the regulation of the blood level by the release of vitamin A from the liver is disturbed. Two factors, therefore, explain the low levels in hepatitis: impairment of intestinal absorption and inability of the liver to release vitamin A. These may be enhanced by insufficient vitamin A intake, especially since carotene is probably not utilized.

Is the low blood level of vitamin A in disease of the liver an indication for treatment with vitamin A? The hepatic concentration of vitamin A cannot determine vitamin A therapy, since vitamin A in the liver is not always available for release. The blood levels, therefore, indicate the vitamin A status and the necessity for treatment. The lack of functional vitamin A is proved by the night blindness associated with acute hepatitis when the liver depots are still normal. The rationale of vitamin A treatment for disease of the liver is evident from

31. Abels, C. J.; Gorham, A. T.; Pack, G. T., and Rhoads, C. P.: J. Clin. Investigation **20**:749, 1941. Abels, J. C.; Rekers, P. E.; Binkley, G. E.; Pack, G. T., and Rhoads, C. P.: Ann. Int. Med. **16**:221, 1942. Abels, J. C.; Gorham, A. T.; Pack, G. T., and Rhoads, C. P.: Proc. Soc. Exper. Biol. & Med. **48**:488, 1941.

32. Breese, B. B., and McCoord, A. B.: J. Pediat. **16**:139, 1940. Ralli, E. P.; Bauman, E., and Roberts, L. B.: J. Clin. Investigation **20**:709, 1941.

33. Murrill, W. A.; Horton, P. B.; Leiberman, E., and Newburgh, L. H.: J. Clin. Investigation **20**:395, 1941.

34. Moore, T.: Biochem. J. **25**:275, 1931. Baumann, C. A.; Riising, B. M., and Steenbock, H.: J. Biol. Chem. **107**:705, 1934.

investigation on rats with experimental damage to the liver produced by carbon tetrachloride or some other poison.[35] In the livers of such rats, vitamin A accumulates in pathologic fat depots and disappears from the normal sites in the morphologically unchanged parenchyma. If moderate amounts of vitamin A are fed to vitamin A–deficient rats intoxicated with carbon tetrachloride, it is primarily taken up by the pathologic fat deposits in the liver. This vitamin A is less readily utilized. Only the feeding of large amounts of vitamin A produces storage in the normal sites also. When the human liver is damaged and vitamin A is stored in pathologic sites from which it is less readily utilized, it is thus desirable to administer extremely large doses of vitamin A. These will first saturate the pathologic areas, with their higher affinity, and then impregnate the normal sites. In addition, such large doses compensate for the disturbed intestinal absorption. That such large doses actually increase the amount of vitamin A in the liver and in the blood has been shown by our feeding experiments with 500,000 U. S. P. units of vitamin A and by those of others.[30] Our present experiences, however, do not allow us to state exactly the quantity indicated when the liver is damaged.

The morphologic demonstration of impairment of hepatic function is still in an unsatisfactory state, not far ahead of clinical tests of hepatic function. The morphologic demonstration of central necrosis with or without imbibition of bile or dispersed miliary necrosis proves that just a small amount of hepatic parenchyma has been put out of function. Since only a fifth of the hepatic parenchyma is sufficient to carry out the function of the liver, the opinion that these small necrotic areas indicate general hepatic damage assumes without evidence that the histologically intact liver is also damaged. Generalized disturbance of the structure of the liver, like the diffuse toxic edema [29] or dissociation of the hepatic cell cords, is found in patients with or without disease of the liver. The only definite signs of diffuse damage to the liver seen in routine histologic study are diffuse interstitial hepatitis and diffuse necrosis of hepatic cells, as in acute yellow atrophy. If exact cytologic studies are omitted—as they usually are—no morphologic evidence for diffuse damage to the liver can be offered and hence the difficulty in correlating clinical tests with the results of routine histologic examination. Whether the 3 patients previously alluded to in whom localized areas of necrosis were not associated with impaired hepatic function actually had damaged livers is questionable. A generalized rather than focal disturbance of the characteristic pattern of the vitamin A fluorescence is more outspoken than the hard to evaluate changes in visible light. That it is a better index of functional impairment is not proved but seems probable.

In none of the specimens obtained at operation was the distribution of vitamin A as even and regular as in healthy, well fed and quickly killed animals (rats and dogs [36]). Only in a few of the biopsy specimens (characterized by ±) and in some postmortem specimens did the distribution approach the normal. In all others, various degrees of irregularity were present. According to this criterion, the liver was not completely normal in any patient coming to operation. Some aberrations from the norm in the periportal field were found in practically all cases, indicating some past or present injury. All evidence (clinical, routine histologic and fluorescence microscopic) points to definite parenchymatous damage in cirrhosis. Damage to the parenchyma of the liver is also very common with cancer of the biliary passages, where prolonged complete obstruction and/or

35. Popper, H.; Steigmann, F., and Dyniewicz, H. A.: Proc. Soc. Exper. Biol. & Med. **50**: 266, 1942.

36. Popper, H., and Greenberg, R.: Visualization of Vitamin A in Rat Organs by Fluorescence Microscopy, Arch. Path. **32**:11 (July) 1941.

infection are obviously responsible. In our series it was also quite common with cholelithiasis with biliary obstruction. The experience that severe damage to the liver will appear after prolonged biliary obstruction is thus confirmed. Our data would indicate four weeks as the limit before severe hepatitic changes occur. Operation for cholelithiasis with jaundice is hence indicated before the end of this period. With ulcers and carcinoma of the stomach, hepatic damage of only slight degree is encountered.

Our cases of disease of the gallbladder contribute to the old controversy as to whether damage to the liver is present in uncomplicated cholelithiasis.[37] In our material the hepatic fatty changes were more common in the patients with this disease than in the other groups. Whether these fatty deposits without vitamin A fluorescence indicate a choline deficiency, as the fluorescence microscopic picture may suggest,[38] can be proved only by the results of choline therapy. Otherwise the incidence of damage to the hepatic parenchyma is only slightly higher than in the other nonjaundiced patients. Only the changes in the periportal field are somewhat more prominent. Investigations are under way to correct the described limited disturbances of the hepatic parenchyma.

CONCLUSIONS

The concentration of vitamin A in the plasma and in the liver (biopsy specimens) and its fluorescence microscopic distribution in the liver have been compared with the results of tests of hepatic function and the routine histologic picture of the specimens.

The plasma level of vitamin A is low when the liver is damaged and is slightly lowered in carcinoma of the stomach. If gross nutritional deficiency can be excluded, a plasma vitamin A level of zero points to severe damage to the liver. In cirrhosis with jaundice and in obstructive jaundice with hepatic damage, the plasma level is lower and the incidence of zero levels higher than in cirrhosis without jaundice and obstructive jaundice without hepatic damage, respectively.

The hepatic vitamin A concentration is often, but not always, reduced when the liver is damaged.

The fluorescence-microscopic pattern of vitamin A distribution is never completely regular. Severe irregularities, however, were found only in cases of hepatitis, cirrhosis or obstructive jaundice with secondary hepatitis. The milder degrees of disturbances of the microscopic picture are considered to indicate slight hepatic damage, not recognized by means of routine histologic examination.

The low blood level of vitamin A in hepatitis is a sign of functional deficiency of the vitamin explained by impairment of (*a*) the release of vitamin A by the liver and (*b*) the absorption of vitamin A from the intestinal tract.

The rationale of administration of large doses of vitamin A in cases of hepatic disease is to overcome the impaired intestinal absorption and to saturate the pathologic fat deposits in the liver in order to impregnate the normal site.

Fluorescence-microscopic changes in the distribution of vitamin A and changes in the periportal field point to functional impairment of the liver in practically all patients coming to operation because of disease of the upper part of the abdomen.

30 North Michigan Avenue.
30 North Michigan Avenue.
Cook County Hospital.

37. Graham, E. A.: Surg., Gynec. & Obst. **26**:521, 1918. Judd, E. S.: Relation of Liver and Pancreas to Infection of Gallbladder, J. A. M. A. **77**:197 (July 16) 1921. Deaver, J. B.: Sequelae of Biliary Tract Infection, ibid. **95**:1641 (Nov. 29) 1930. Noble, J. F.: Am. J. Path. **9**:473, 1933.

38. Popper, H., and Chinn, H.: Proc. Soc. Exper. Biol. & Med. **49**:202, 1942.

PLASMA CLOT SUTURE OF NERVES

EXPERIMENTAL TECHNIC

I. M. TARLOV, M.D.

C. DENSLOW

S. SWARZ

AND

D. PINELES, M.D.*

BROOKLYN

By plasma clot suture it has been found possible in certain cases to effect better restoration of the anatomic relationships of nerve stumps with less trauma to them than with the aid of silk.[1] However, owing largely to imperfections in technic, our earlier experiments were not uniformly successful. It soon became clear that plasma clot was suitable as suture material only when the nerve ends could be united without tension. It developed that further requisites for satisfactory suture by means of a plasma clot are: freedom from hemorrhage and contusion around the site of suture; procurement of flat, smooth contact surfaces of the nerve stumps so that satisfactory coaptation of fibers can be obtained, and the use of a removable mold which permits the plasma to surround uniformly the entire site of suture.

The results of our efforts to bring about these favorable conditions for plasma clot suture of nerves in animals (rabbits, dogs and monkeys) together with an account of the development of a suitable mold will be given. The use of a special mold for suturing nerve grafts and a combined thread–plasma clot technic for suturing nerves under tension will be described.

OPERATIVE APPROACH TO THE SCIATIC NERVE

In our early operations on dogs, the sciatic nerve was exposed by an incision high in the posterior part of the thigh which split the biceps femoris muscle. In spite of the care which was taken to avoid trauma, some tearing of muscle fibers with bleeding occurred, both of which factors tended to increase the inflammatory and fibrotic reaction at the site of suture. A search for another approach to the sciatic nerve was made, and it was found that by making the incision of the skin laterally over the femur and incising the thin fascial extension of the biceps muscle one encounters a plane of cleavage between the biceps and the vastus lateralis muscle. By retracting the former mesially the sciatic nerve is exposed, and it may then be freed from the surrounding structures. Practically no tearing of muscle fibers follows this procedure, and by means of it the nerve can be exposed from a point 1 to 2 cm. distal to its exit from the pelvis to the popliteal fossa. All bleeding vessels should be caught and tied with fine silk ligatures. Since a bloody operative field promotes cicatrization at the site of suture, complete hemostasis is imperative.

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* Fellow in Surgical Research.

From the Neurosurgical Service and the Department of Laboratories, the Jewish Hospital.

This work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the Jewish Hospital of Brooklyn. The work was also aided by a grant from the Committee on Scientific Research of the American Medical Association.

1. Tarlov, I. M., and Benjamin, B.: Plasma Clot and Silk Suture of Nerves, Surg., Gynec. & Obst. **76**:366, 1943.

METHOD OF CUTTING AND ARRESTING BLEEDING FROM THE SCIATIC NERVE

Our former method of cutting the sciatic nerve consisted in elevating it, holding it taut by means of a nerve hook and severing it with a new razor blade. There were two chief disadvantages with this method: First, the amount of tension exerted on the nerve during its elevation and section in all probability resulted in damage for some distance from the cut. In the second place, the cut surfaces of the stumps were frequently uneven or one bundle of the nerve would retract more than another so that only incomplete contact of the stumps could be effected by means of plasma clot suture. Our present technic requires the use of a special nerve holder, the

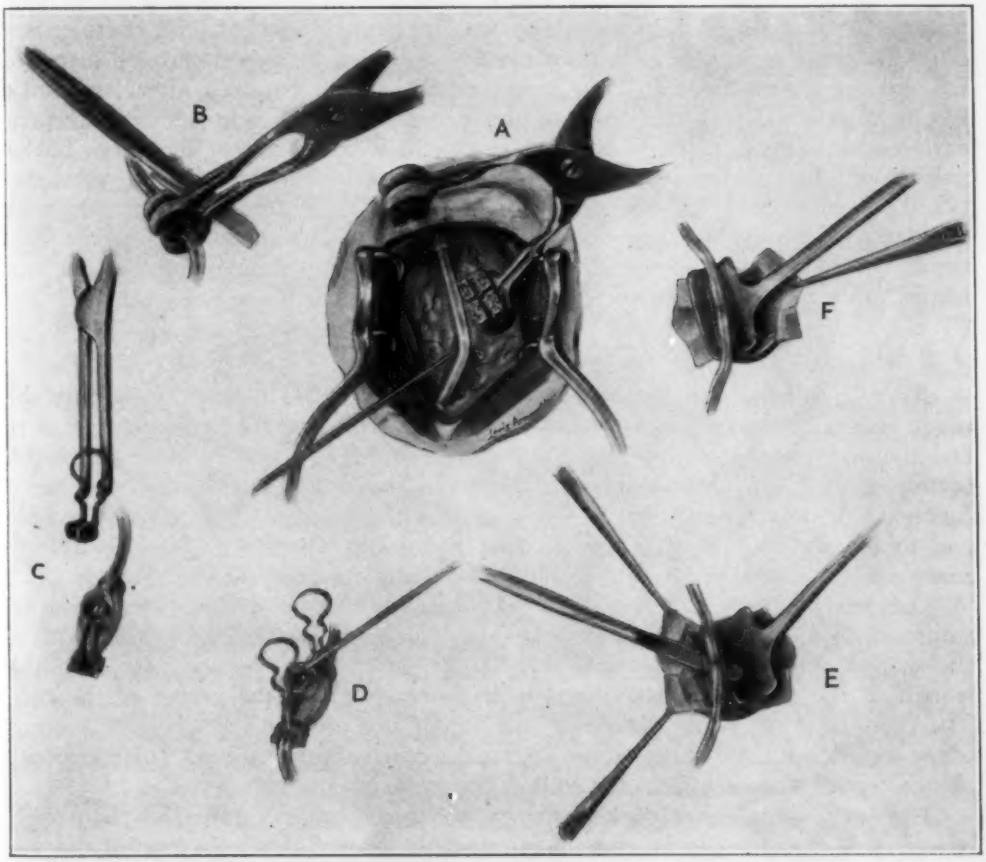

Fig. 1.—Series of sketches illustrating the technic of cutting the sciatic nerve and suturing it by means of plasma clot.

purpose of which is to hold the nerve securely while it is being cut. The device operates in a manner similar to a pair of scissors, but instead of cutting blades it has two arms equipped at the tips with opposed curved jaws covered with air-foam rubber, into which a groove is cut to accommodate the nerve (fig. 1 *A* and *B*). The use of the layer of air-foam rubber within the jaws of the instrument makes it possible to hold the nerve firmly without traumatizing it. A lengthwise slot about 25 mm. long and 0.5 mm. wide passes through the center of the jaws and the arms of the nerve holder to allow a razor blade to slide through and cut the nerve. The piece of razor used consists of one half of a Gillette type blade which

has been broken lengthwise and mounted on a needle holder. By this means one is enabled to obtain fairly flat cut surfaces on the nerve stumps, which permit a more accurate apposition of the severed ends. Furthermore, the danger of trauma to the nerve from tension, such as attended the use of the nerve hook, is eliminated. Also it was observed that there is less bleeding from the nerve stumps with the new technic.

Bleeding from the nerve stumps was controlled in our original experiments by means of gentle pressure with cotton pledgets. However, subsequent examination of the site of suture not infrequently disclosed infiltration with monocytic cells and giant cells around cotton fibers remaining adherent to the nerve. This tissue reaction made it difficult to assess the results of plasma clot suture in such instances. The use of cotton pledgets was therefore discarded, and the bleeding from the nerve stumps is now more readily controlled by means of small pieces of crushed autologous muscle. The pieces of muscle are removed after hemostasis has been attained. If contusion of the nerve ends has occurred or if the cut surfaces are ragged, a thin slice may be excised with the aid of the nerve holder and razor. Flat surfaces of the severed ends are essential for satisfactory coaptation. After a nerve has been divided, retraction of the epineurial sheath, with resultant prominence of the bundles of nerve fibers, sometimes occurs. This condition does not seem to retard successful regeneration following plasma clot suture, since a new connective tissue sheath is formed in the plasma clot.

USE OF RUBBER MOLDS FOR SUTURING NERVES WITH PLASMA CLOTS

At first, plasma clot suture on rabbits was performed merely by holding the nerve ends in apposition at the base of a trough formed by the neighboring tissues and then adding the plasma followed by the clotting agent. The main limitation of this method was that the plasma clot coated only the upper half of the nerve junction. It became clear that in order to make the union more secure, the technic had to be modified in some way so that the site of suture could be completely surrounded by the clot. A rubber mold was finally designed for this purpose.

Our early efforts at making a mold for containing the plasma at the site of suture resulted in a hollow tube wide open along its entire extent and with a cup-shaped depression in the center (fig. 2 *A*). The nerve was placed in the trough of the mold with the junction of the ends above the center of the cup. The chief fault with this mold was that it did not provide for adequate coating of the superior surface of the nerve. After the central cup was filled, any additional plasma tended to escape from the ends of the mold.

The next step in design of the mold was the introduction of gates into the trough on each side of the cup in an attempt to retain the plasma above the level of the line of suture (fig. 2 *B*). The gates were cut at one side to allow for removal of the mold after clotting of the plasma occurred. This type of mold proved unsatisfactory, because unless the openings under the gates were of exactly the same size as the nerve to be sutured the plasma escaped from these points. The next major step came with the development of a spherical mold with sleeves attached to envelop the nerve ends (fig. 2 *C*). An opening was cut in the top of the mold to permit manipulation of the nerve stumps and introduction of the plasma. A slit was made extending from the opening to the ends of the sleeves to allow for the application and removal of the mold. Leakage of plasma at the ends of the sleeve still occurred occasionally because of the variation in the size of the nerves to be sutured. Parallel fins of latex were then built upward from the slit (fig. 2 *D*). The fins were clamped together to obtain a closer fit around the nerve. Still leakage of plasma

from the ends of the sleeves sometimes occurred or else there was the possibility of damaging the nerve by too tight constriction of it in the sleeves.

At this point an experiment in a new type of mold was tried. A rigid aluminum mold was made on a lathe in two halves and held together by special metal hinged clips (fig. 2 *E*). It was thought that the construction of the mold in two halves, rather than in one piece, as in the case of the rubber molds, might facilitate its removal after clotting of the plasma had occurred. In the aluminum mold an oversized space was left in the sleeve and a layer of air-foam rubber inserted. The air-foam rubber afforded maximum cushioning effect on the nerve and prevented leakage of plasma around it. The difficulty in adjusting the four pieces of metal around the site of suture and the rigidity of the entire mold led us to discard it. However, the use of the air-foam rubber collar proved most helpful in solving the problem of constructing a rubber mold (fig. 2 *F*) suitable for use with nerves of a limited variety of sizes and also in preventing leakage of plasma from the ends of the mold without injurious constriction of the nerve. The air-foam rubber was

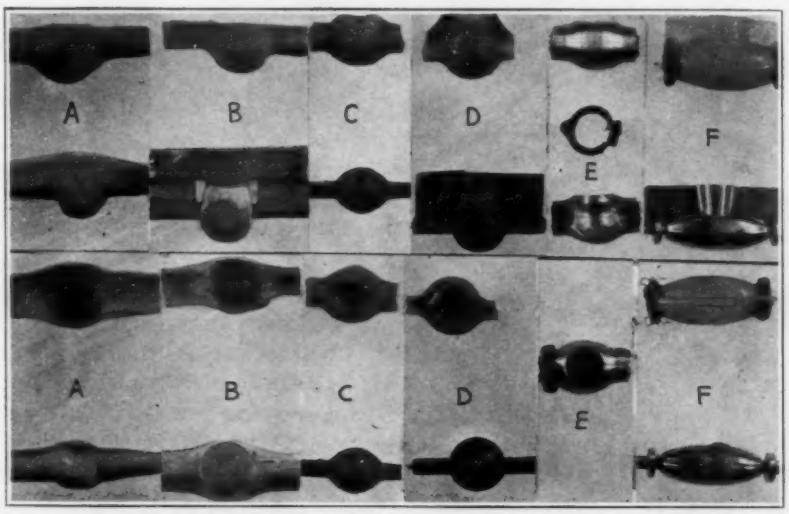

Fig. 2.—Photographs of the various molds and the models from which they were formed tried out in the development of the present mold used for suturing peripheral nerves. The two upper rows are side views; the two lower rows, top views.

thus incorporated into our rubber molds. The rubber molds, moreover, were made with a funnel opening on top so that when preliminary tests of plasma showed marked clot retraction an extra drop or two of plasma could be introduced into the funnel reservoir to insure that the clot would adequately cover the top of the suture. Another advantage of the funnel reservoir is that in those instances in which the plane of the nerve to be sutured is not perfectly horizontal the entire body of the mold can, nevertheless, be completely filled by introducing plasma to the top of the funnel.

The mold in its present form is shown in figure 3. In the sketch, *W* represents the wire supporting rails along which the nerve ends are placed. These supporting rails are threaded through wire loops in the base of the air-foam rubber collar, *A*. To hold the handles of the rails in place so that they can be easily grasped and removed during the operation, two wire loops (*L*) are placed on the outside of the air-foam rubber collar at one end of the mold. The loops are bent outward

so that they do not protrude unnecessarily far from the collars. The rails are made just long enough to reach from end to end of the mold. They are bent in the form shown. In the portion of the handle that fits into the loop is a series of ridges which prevents the rails from slipping out of place. The distance between the rails must not be too wide or the nerve ends may slip between them to the bottom of the mold. In order to facilitate insertion of the wire rails through the loops in the air-foam rubber collars, the shaft of a 26 gage hypodermic needle broken off from the hub and with its point blunted is used. The rails are threaded through these metal tubes after the latter have been introduced through the loops. The tubes are then withdrawn from the mold and the rails left in place.

In order to suture a nerve with plasma clot, one end of it is introduced into the mold with its cut surface in the center of the bowl (fig. 1 *C*). A metal clip (*C*) is applied to the fins (*F*) of the mold as close as possible to the collar. The clip thus tightens the grip of the collar around the nerve, preventing retraction of the nerve and leakage of plasma around it. The other end of the nerve is placed in the mold after the fins are spread apart by a forceps to facilitate introduction. When

Fig. 3.—Diagrammatic sketch of the mold used at present.

satisfactory apposition of nerve ends has been obtained, a metal clip is applied to the fins at the other end of the mold. Plasma is then introduced into the mold through the funnel (*N*) (fig. 1 *D*). The large dorsal artery on the sciatic nerve serves as a convenient guide for maintaining the proper axial relationships between the central and peripheral nerve segments.

Before the use of the wire supporting rails was introduced, the nerve ends were held together with a small jeweler's forceps for about five minutes or until clotting had occurred. It was found to be very difficult to hold the nerve stumps together without any movements for this period of time, and, moreover, withdrawl of the forceps resulted in defects in the clot. The use of the wire supporting rails overcame these difficulties and enabled us to obtain better apposition of nerve ends. About twenty minutes after clotting occurs, which is the time required for plasma clots to achieve their maximum stability,[2] the wires are withdrawn by inserting

2. Goldfarb, A. I.; Tarlov, I. M.; Bojar, S., and Wiener, A. S.: Plasma Clot Tensile Strength: Its Relation to Plasma Fibrinogen and to Certain Physical Factors, J. Clin. Investigation **22**:183, 1943.

forceps into the handles (*H*) of the wire rails and the metal clips are removed. The rails are made of very flexible no. 34 nickel silver wire, which may be curved acutely during their withdrawal without danger of their ends cutting the plasma clot.

The removal of the mold from the site of suture was the source of considerable difficulty in our earlier experiments. Finally an instrument was made by cutting down a teaspoon to the length of the mold and making it slightly concave to correspond to the shape of the clot around the junction in the nerve. After the clot is freed from the mold with the use of a small dissecting instrument, the fins of the mold are grasped by an assistant and held back. The spoon is then inserted between the mold and the sutured nerve (fig. 1 *E* and *F*). The nerve is gently elevated by the spoon and thus protected during the withdrawal of the mold by the assistant.

In those occasional instances in which the latex mold cannot be used because of the extreme smallness of the nerves or the lack of sufficient space, plasma clot suture can be used if one employs the original, cruder, technic described, namely, merely depressing the nerve ends into the neighboring tissues to form a trough in which the plasma can collect. As already mentioned, the ends must be held together with a fine forceps until clotting occurs.

EXPERIMENTS TO DETERMINE THE MOST SUITABLE SHAPE AND SIZE OF MOLD

After a suitable mold for retaining the plasma uniformly around the site of suture was developed, our attention became focused on the problem of distributing a given amount of plasma in such a way as to lend maximum support to the sutured nerve. The first question that arose was whether the basic shape of a mold would affect appreciably the strength of the nerve union. In order to test this point, experiments were performed in vitro on segments of freshly removed nerves sutured with autologous unmodified plasma in molds which were round, diamond shaped or fusiform. The nerves (all of the same general caliber and length) and the plasma were obtained from dogs, and the molds were all of approximately 15 drop capacity. The molds were so designed that 3 to 5 mm. of the nerve to each side of the suture was included in the plasma clot. The tensile strength of the sutured nerve was tested by the method described [4] for testing plasma clots. Six tests were made with nerves sutured in each mold. The average weight load held by the nerve sutured in the fusiform mold was 22.5 Gm.; in the round and the diamond-shaped mold, 15 Gm. each. There is some indication, then, that the fusiform mold represents the best of the three shapes tried, since the junctions formed in it appear to be strongest.

The fact that the nerve slipped out of the clot rather than broke at the site of suture when the maximum weight was exceeded indicated that it might be possible to strengthen the union of the sutured nerve by increasing the segment of nerve gripped by the plasma, even though this entailed a reduction in the maximum diameter of the clot. Accordingly, three other fusiform molds of the same capacity were made and so shaped that 7 mm., 9 mm. and 11 mm. respectively of nerve on each side of the suture was gripped by the plasma clot. The average tensile strength of the nerve sutured in 17 tests in the mold of 10 mm. inside length was 24.1 Gm.; in 26 tests in the mold of 14 mm. size, 27.1 Gm.; in 27 tests in molds 18 mm. long, 28.5 Gm.; in 6 tests in 22 mm. molds, 25.8 Gm. The clot slipped off the

3. Footnote deleted.

4. Tarlov, I. M.; Goldfarb, A. I., and Benjamin, B.: A Method for Measuring the Tensile Strength and Stretch of Plasma Clots, J. Lab. & Clin. Med. **27**:1333, 1942.

nerve in every instance in which the nerves were sutured in the 10 mm. mold, while it invariably broke at the site of suture when the 22 mm. mold was used. These results indicate that the manner of distribution of a given amount of plasma affects the tensile strength of the sutured nerve to only a slight extent. Somewhat greater values for tensile strength were obtained with the 14 mm. and 18 mm. molds, and with them a balance seemed to have been reached between the point at which the clot slipped off the nerve and that at which the clot broke at the site of suture. Relatively little difference in the average weight load held before separation appeared at the site of suture occurred with the different molds, the average reading being about 8 Gm.

Experiments were then done to determine the effect of the amount of plasma on the tensile strength of the suture. A mold intermediate in size (16 mm.) between the 14 and 18 mm. ones was used as a basis for calculating the dimensional relationships for molds of larger capacities, since this mold required somewhat less exposure at operation than the 18 mm. mold. The ratio of inside diameter to length of the 16 mm. mold was 1 : 2.3. On the basis of this ratio, fusiform molds of the following approximate capacities were made: 7 drops; 13 drops; 25 drops; 36 drops; 45 drops; 90 drops. Nerves were sutured in vitro with use of these

Relationship of Capacity of Mold to Tensile Strength of Nerves Sutured with Plasma Clot

Capacity of Mold, Drops of Plasma	Average Weight Load Held Before Complete Separation Occurred at Site of Suture, Gm.	Average Weight Load Held Before Visible Separation Occurred at Site of Suture, Gm.	Number of Tests
7	16.3	2.5	8
13	30.6	5.6	9
25	36.3	9.2	6
35	60.3	16	6
45	68.6	?	11
90	83.6	?	7

molds, and tests of tensile strength of the sutured nerves were made. The results are shown in the table.

The average load which the nerve held before visible separation occurred at the site of suture was difficult to determine with the two largest molds, since the opacity of the large clots obscured the suture. Although considerable variation occurred in the tensile strength of nerves sutured with a given amount of plasma, the tendency toward a rise in weight load held with the increase in quantity of plasma which surrounded the nerve junction was fairly consistent in each series of determinations. These results are supported by previous test tube experiments which showed that the tensile strength of clots is directly proportional to their cross-sectional area.[2] From the standpoint of the strength of a sutured nerve, then, the greater the quantity of plasma used, the better the result. However, the limiting factor in determining the suitable amount of plasma that could be used proved to be the resultant histologic reaction.

Fifty-seven sciatic nerves were sutured in the six molds of different capacities, holding quantities of plasma which varied from 6 to 90 drops. The animals either died or were killed three to fifty-seven days after operation, and a quantitative comparison of the histologic reactions at the sites of suture was attempted. There was a lack of complete uniformity in the results, which suggested that one or more factors other than the quantity of plasma used tended to promote inflammation and fibrosis at the site of suture. Our experiments indicated that these factors

are trauma to the nerve ends or to surrounding tissue and hemorrhage during the operation. In certain instances these factors had more than offset the effect of the quantity of plasma used. Nevertheless, as a rule, it was found that with amounts of plasma up to 20 to 25 drops there followed minimal histologic changes, characterized by the appearance of a few polymorphonuclear leukocytes, lymphocytes, monocytic cells, plasma cells, fibroblasts and thin-walled blood vessels. In most of the operations in which 90 drops of plasma was used and, to a much less extent in those in which 45 drops of plasma was used, considerable inflammatory reaction and, later, fibrosis ensued. Histologic changes of moderate intensity occurred with amounts of plasma in the intermediate range. Accordingly, approximately 20 drops of plasma was considered as a suitable amount for suturing the sciatic nerves of dogs. With care in performing the operation, somewhat larger quantities may be safely used.

THE USE OF DRIED PLASMA AND PURIFIED FIBRINOGEN FOR CLOT SUTURE OF NERVES

Autologous plasma was used for the sutures although homologous plasma would probably serve as well for this purpose. Our experiments have thus far revealed no difference in the degree of tissue reaction following suture with autologous and with homologous plasma clots. It has been our practice to use unmodified plasma (i. e. plasma to which no anticoagulant has been added), which is allowed to clot spontaneously, since it has been found that the addition of anticoagulants or coagulants to the plasma results in clots of diminished strength. In order to obtain unmodified plasma, the blood is collected in chilled paraffin-lined tubes packed in ice and centrifuged in large metal cups filled with ice; the plasma is then transferred to test tubes coated with paraffin and again packed in ice. In view of the inconveniences involved in the procurement of fluid unmodified plasma, experiments were undertaken in an attempt to prepare dried unmodified plasma which would not require a coagulant for clotting. The commercial dried plasma when dissolved in distilled water and recalcified yielded clots of rather low tensile strength. We have obtained dried plasma from dogs' unmodified plasma by the process of dehydration under high vacuum in the frozen state. However, like Strumia,[5] we found that as a result of the drying process, the p_H of the plasma after being redissolved is increased and thereby the activity of the prothrombin is diminished, with resultant failure of spontaneous clotting. The addition of acid to the solution of dried plasma is necessary in order to restore the original p_H of the plasma and thus reactivate the prothrombin so that clotting can occur. In fact, after restoring the dried plasma to its original volume by dissolving it in distilled water and adding a small amount of dilute hydrochloric acid, fairly prompt clotting has been obtained and the clots proved to be almost as strong as those prepared from the original sample of fluid plasma. Hypertonic solutions of the dried plasma to which sufficient hydrochloric acid has been added to lower the p_H to approximately 7.4 have yielded some clots of greater tensile strength than those prepared from the original sample of plasma. Satisfactory nerve sutures have been obtained in dogs with clots prepared from dried unmodified plasma.[6]

Nerve sutures have been performed on dogs with clots formed from human fibrinogen and thrombin.[7] Although clots prepared from these materials provided sufficient holding power for the nerve ends when tension was not present at the

5. Strumia, M.: Preservation of Prothrombin in Dried Plasma, J. A. M. A. **119**:710 (June 27) 1942.

6. The experiments with dried plasma are now being carried on with the assistance of Dr. A. E. Sobel and Mr. M. Rockemacher.

7. Supplied by Professor E. J. Cohn, Harvard University.

site of suture, unlike plasma clots they underwent some degree of lysis after twenty-four to forty-eight hours. This disadvantage is serious, since lysis of the clots may be followed by detachment at the site of suture because union of the nerve ends does not occur within this time. If this objectionable feature can be overcome, then fibrinogen-thrombin clots prepared from homologous blood may prove to be desirable as suture material for nerves. For the present, fresh fluid unmodified plasma seems preferable, although clots prepared either from dried plasma or from fibrinogen and thrombin may prove superior in the near future.

TECHNIC OF COMBINED PLASMA CLOT AND TANTALUM WIRE (OR SILK) SUTURE FOR NERVES UNDER TENSION

When nerve ends cannot be united without tension being present at the junction, then plasma clot suture is inadvisable since the risk of subsequent detachment at the site of suture is too great. It was suggested to one of us (I. M. T.) by Lieut.

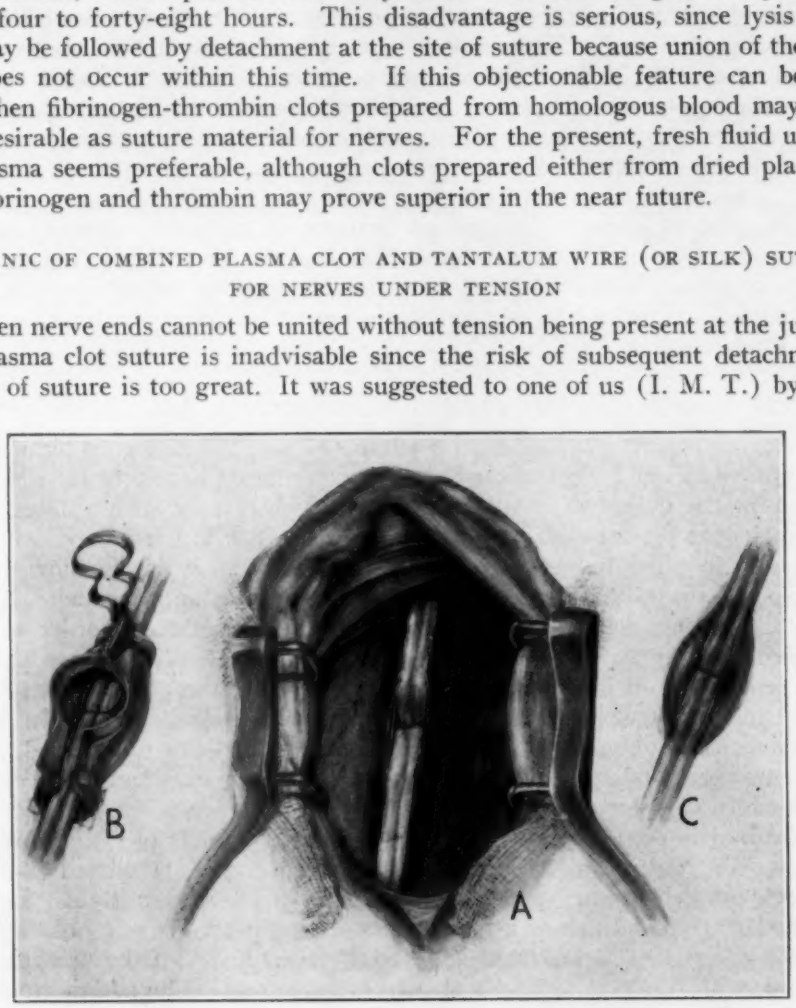

Fig. 4.—Technic of suturing a nerve under tension by use of tantalum wire and plasma clot.

Col. R. Glen Spurling that in those instances in which tension exists at the site of suture, fine tantalum wire [8] (0.0025 or 0.0030 inch [0.0064 or 0.0076 cm.] in diameter) be used as tension sutures to approximate the nerve ends and plasma clot then used to achieve their accurate apposition. This suggestion was followed, and in other instances single strands of 00 Corticelli black silk untwisted into its three component strands were used instead of the tantalum wire. The wire or silk, threaded on fine curved ophthalmic needles, is introduced through the epineurium, one on each side of the nerve at the plane of its greatest diameter and at a distance of about 1 cm. from the ends of the nerve. The silk or wire is tightened until the nerve ends can be approximated without tension, and each is tied well away from the junction (figs. 4 *A* and 5 *A*). When one is dealing with small nerves which contain delicate connective tissue sheaths, some nerve fibers must be included in each bite of the suture in order to obtain sufficient hold on the

8. The Fansteel Metallurgical Corporation supplied the tantalum wire.

nerve to overcome the amount of existing tension. The nerve is then placed in the mold, the ends accurately adjusted on the wire rails (figs. 4 *B* and 5 *B*), the clips applied and the plasma introduced in the usual manner. By means of plasma clot suture, one is enabled to obtain more accurate coaptation of the cut surfaces without the buckling of nerve fibers or the distortion of nerve pattern that is apt to occur when any type of thread suture is used in an attempt to restore the anatomic relationships of a divided nerve. The two wire or silk sutures used to remove the tension from the suture are incorporated in the plasma clot (fig. 4 *C* and 5 *C*). The degree of inflammatory reaction is less with tantalum wire than with silk, and, moreover, the tantalum is stronger. Detachment at the suture site has been observed once in a series of 16 operations in which silk tension sutures were used in conjunction with plasma clot suture: in this one instance the silk sutures had broken. Breakage of the wire or separation at the suture site has not occurred in any of the 10 instances in which the tantalum wire–plasma clot technic

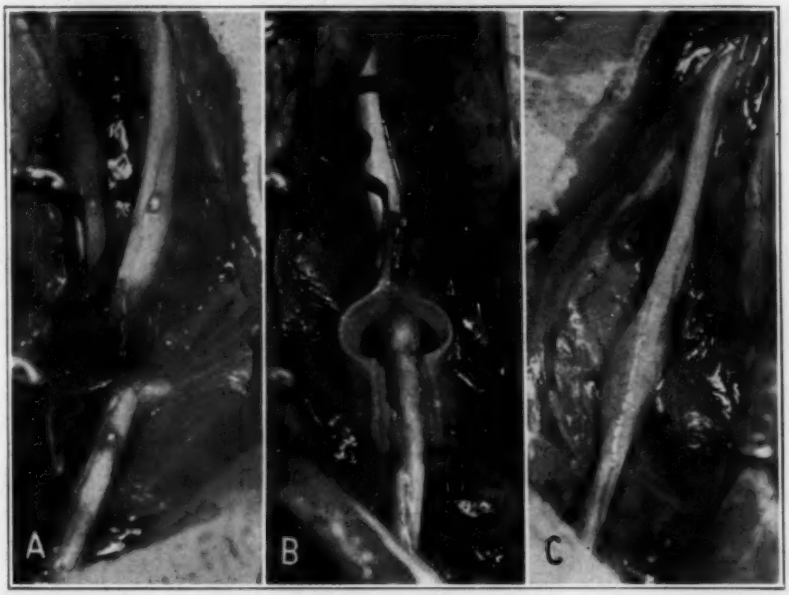

Fig. 5.—Photographs taken at operation, showing the ends of the nerve approximated (*A*) by means of two tantalum wire sutures, accurately apposed (*B*) in the mold (one clip already in place) and sutured (*C*) with plasma clot. The tantalum wires are incorporated in the clot.

was used. Excellent apposition of nerve ends (fig. 6 *A*) with minimal tissue reaction (fig. 6 *B* and *C*) occurred with the use of this method.

It is to be emphasized that under conditions in which a great deal of tension exists at the site of suture the chance of successful results following any type of suture is probably small, and under such circumstances the insertion of some type of nerve graft should be considered.

TECHNIC OF SUTURING NERVE GRAFTS

If, owing to loss of nerve substance or to marked retraction, the ends cannot be apposed by the usual methods for diminishing nerve defects, such as the free mobilization of the ends or the flexion of a joint in order to relax a nerve, or by transposition of a nerve for the purpose of shortening the route that it must take,

then the insertion of some type of graft should be considered. If one accepts the prevailing viewpoint, that in order for satisfactory regeneration to occur a graft must contain viable Schwann cells—and there are good grounds for this belief [9]—then the use of grafts fixed in solutions, such as alcohol or a solution of formaldehyde, is to be condemned. One must focus, then, on the possibility of employing

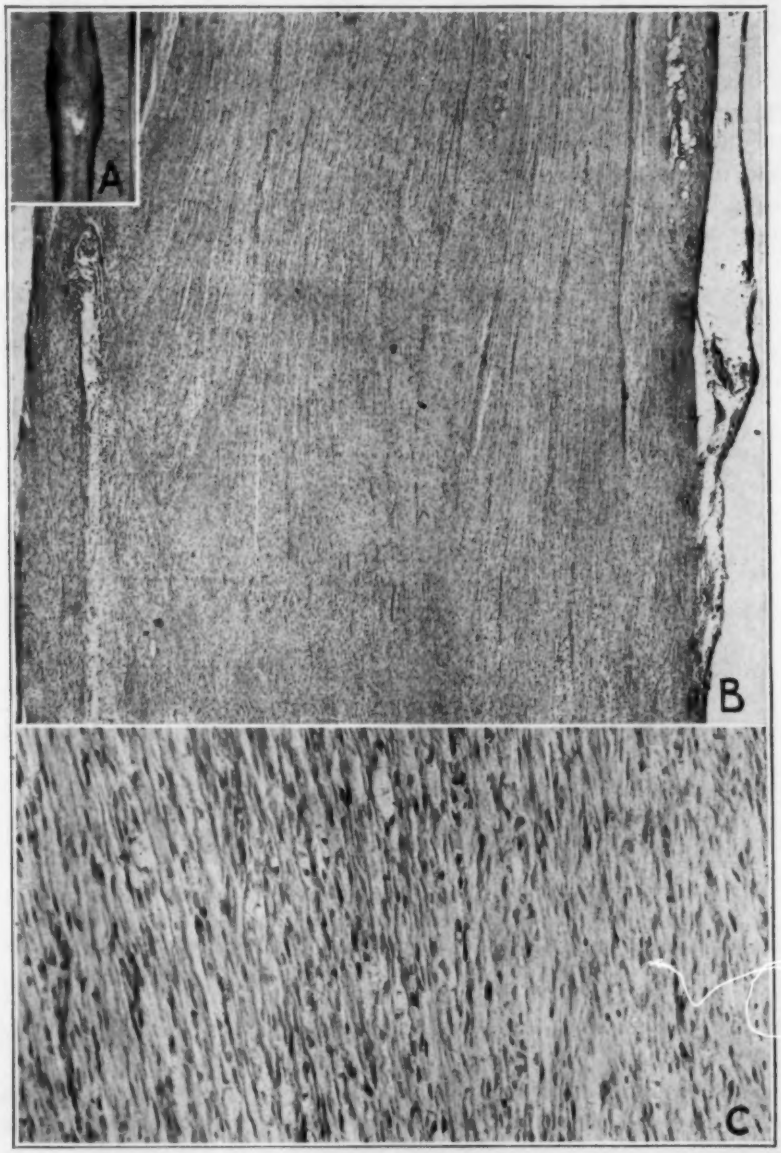

Fig. 6.—*A*, gross appearance of the sciatic nerve of a dog thirty-eight days after suture with tantalum wire and plasma clot; *B*, and *C*, photomicrographs from the site of suture, showing practically no inflammatory or fibrotic reaction. The sections were stained with hematoxylin and eosin (*B*, × 32; *C*, × 180).

9. Young, J.; Holmes, W., and Sanders, F.: Nerve Regeneration: Importance of the Peripheral Stump and the Value of Nerve Grafts, Lancet **2**:128, 1940.

viable nerve transplants. As was to be expected in view of the high degree of specificity of mammalian tissues, heterologous nerve grafts have not proved successful. Although the possibilities of using viable homologous nerve grafts have not yet been thoroughly explored, experimental laboratory and clinical observations suggest that the most satisfactory results may be obtained with the use of autologous grafts. When defects exist in large nerves, the only type of autologous graft that could be considered is the cable transplant, since with a human subject there would be no justification for sacrificing one major functioning nerve for another. In cable transplantation, several segments of a nerve which can be sacrificed without serious resultant defect are used. These segments are placed side by side until their combined cross-sectional area approximates that of the nerve to be repaired. A tubular mold made of latex and containing the inside shape and transverse measurements of the desired cable has proved useful for the formation of the cable graft. The nerve segments are glued together by means of a thin coat of plasma applied with a pipet. The graft should be made a few millimeters longer than required, so that a thin slice can be excised in order to obtain a flat contact surface for apposition with the freshly cut ends of the nerve stumps of the host.

To facilitate the introduction and suture of a nerve graft, a special tandem (twin) mold was made. The mold consists of two of the single molds already

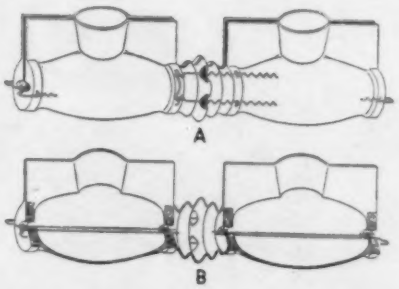

Fig. 7.—Sketches of the exterior (*A*) and interior (*B*) of the twin mold used for suturing nerve grafts by means of plasma clot. Recently 16 gage spring sheet nickel silver has been used to make the adjustment regulators. The closed ends of the U are fastened with fine wire to the outside of one of the air-foam rubber collars next to the adjustment bellows. The prongs are made so that they spring slightly apart, thus causing notches cut 1 mm. apart on the outer side of each prong to catch on the sides of the wire loops.

described with a bellows between them, all made into one piece (fig. 7). The distinctive feature of the tandem mold is the bellows, which allows of some adjustment between the two main body parts of the mold in order to accommodate grafts of varying sizes. The bellows is similar to a miniature camera bellows but circular in form, wider at the center and tapering at both ends. This mold permits the insertion of the graft into it before the mold is placed into the operative site between the nerve ends, thus rendering the procedure simpler than it would be if attempted with two single molds. The distances between the centers of the two main parts of the body of the mold with bellows collapsed and extended are 30 and 40 mm. respectively. The mold can therefore be used for grafts which vary in length from 3 to 4 cm. For longer grafts bellows of correspondingly greater lengths may be used. Grafts of 2.5 and 3 cm. in length may be sutured in special twin molds which contain, instead of the median bellows, a single median air-foam rubber collar, the width of which depends on the length of the graft. Grafts of less than 2.5 cm. in length may be sutured in single molds

which contain two funnels, one above the site of each suture, the mold being longer than the single mold previously described but somewhat constricted in the center. In order to adjust the tandem mold to a desired length and prevent tension on the graft or the sutures, two U-shaped wires with undulations along their prongs are slipped through small wire loops in the proximal collars of the mold. A notch is cut away from the central fold of the bellows so that it will clear the wires. Because of angulation of the undulations, the adjustment wires prevent change in length when the bellows has been placed in a certain position. The wire supporting rails on which the nerve ends rest, as used in the single mold, are contained in each half of the mold.

After the ends of the nerve graft are properly apposed to those of the host nerve, the four metal clips are applied to the fins as close as possible to the air-foam rubber collars and the plasma introduced through each funnel. After complete clotting has occurred, the wire supporting rails are withdrawn, the clips are removed and the mold, freed from clot and nerve in the usual way, is withdrawn with the aid of a spoon the length of the mold. A graft sutured in this way is shown in figure 8.

Fig. 8.—Photograph taken at operation on a dog, showing a single homologous cadaver graft sutured with plasma clot. Pronounced retraction of the clot has occurred, so that there is little excess clot left around the sites of suture.

COMMENT

The most important factors in the technic of suturing nerves are the accurate restoration of fascicular topography and the utilization of materials and methods which result in the production of a minimum amount of cicatrization at the site of suture. An apparently perfect end to end approximation of the severed nerve ends may result in incomplete functional recovery if torsion of the stumps has occurred, because regenerating motor nerve fibers might enter channels leading to sensory end organs and conversely. It seems likely that such misdirection of nerve fibers accounts for many of the defective end results from nerve suture. Although accurate alinement of nerve fibers in a microscopic sense is probably impossible to achieve, a closer approach to this ideal may be obtained with plasma clot than with silk suture. The nerve ends can be adjusted in the mold before the clips are applied, and more exact alinement can be made, even after the clips have been applied, by utilizing the slight natural stickiness of the nerve ends to maintain the relationship of the stumps until the plasma is added and the junction

made more secure. Unless loss of nerve substance has occurred, matching of blood vessel markings, longitudinal striations or nerve bundles makes it possible to restore the proper axial relationships of the nerve stumps when plasma clot suture is used. Such realinement of nerve trunks is not as readily achieved by means of silk suture, since it is difficult to place each stitch at exactly corresponding circumferential points along the stumps. As a result some degree of torsion is likely to occur; moreover, crowding of nerve fibers, with distortion of nerve pattern, frequently occurs when the threads are tied.

Careful attention must be devoted to the prevention of scarring at the site of suture, since such proliferative changes in connective tissue constitute a considerable hindrance to the downgrowth of nerve fibers. The use of fine silk thread confined to the epineurium results in relatively little inflammatory and subsequent fibrotic reaction at the site of suture. However, in the case of small nerves which possess delicate connective tissue sheaths, it is difficult or impossbile to confine the stitches to the epineurium, and strangulation of nerve tissue with subsequent necrosis and fibrosis frequently results. Young and Medawar [10] have sought to overcome this dlifficulty by introducing the use of fortified cockerel plasma and chick embryo extract for the purpose of joining ends of divided nerves. Our studies [11] have shown that autologous plasma is superior to cockerel plasma and chick embryo extract as suture material in that less inflammatory and fibrotic reaction occurs. Autologous plasma compares favorably with and usually surpasses fine black silk suture in respect to the small amount of resultant inflammation and scarring.

The use of plasma clots obviates much of the cicatrization resulting from strangulation of tissue which accompanies the use of any type of thread suture employed for the purpose of bringing nerve ends into apposition. The greater degree of handling of the nerve ends entailed by the use of thread rather than clot suture contributes to the trauma and scarring of tissue at this site. It is to be expected that with careful technic in the execution of autologous plasma clot suture formation of scar tissue at the site of junction may be reduced to a minimum.

It must be borne in mind that the real test of the value of a new technic for suturing nerves is not the type of histologic reaction that occurs at the suture site nor the appearance of numerous nerve fibers in the peripheral stump but rather the degree to which restoration of function to the innervated part occurs. In this connection, it should be stated that several dogs on which plasma clot suture of the sciatic nerve was done on one side and silk suture on the other side have shown almost complete restitution of normal gait. In these few animals there has been as yet no consistent difference in the rate or degree of recovery of function which could be attributed to the different methods of suture. However, the superior gross and histologic results associated with plasma clot would lead one to anticipate correspondingly better functional return to the innervated part than with silk suture; further correlative studies will be necessary to test this point.

CONCLUSIONS

When performed in the manner described, autologous plasma clot suture of peripheral nerves has proved experimentally to be a useful procedure in those

10. Young, J. Z., and Medawar, P. B.: Fibrin Suture of Peripheral Nerves, Lancet **2**:126, 1940.

11. Tarlov, I. M., and Benjamin, B.: Autologous Plasma Clot Suture of Nerves, Science **95**:1258, 1942; footnote 1.

instances in which the stumps can be approximated easily without any tension. It is possible to obtain more accurate apposition of nerve ends with better restoration of fascicular topography by this means than with thread, and, moreover, less scarring is apt to occur at the junction. Good functional return to the innervated part follows the use of this technic on dogs.

When a moderate degree of tension does exist at the line of suture, it is still possible to utilize the advantages of plasma clot suture by combining this technic with the use of very fine tantalum wire tension sutures. The thread sutures are introduced well away from the cut surfaces of the nerve and serve to eliminate the factor of pull from the nerve junction.

A tubular mold has been found useful for the formation of cable grafts from single strands of nerve glued together with clotted plasma. The technic of suturing single or cable grafts is greatly facilitated by the use of the twin mold described.

Miss Dorothea Denslow, director of the Clay Club of New York, assisted in the development of the mold for use in the technic of plasma clot suture. Miss Ruth Kaslow assisted at the operations and in the postoperative care of the animals.

MECHANISM OF ERYTHREMIA

ERYTHREMIA RESULTING FROM TRAUMATIC SHOCK IN DOGS AND FROM INJECTIONS OF EPINEPHRINE INTO HUMAN BEINGS AND DOGS

R. D. TAYLOR, M.D.
AND
IRVINE H. PAGE, M.D.
INDIANAPOLIS

Epinephrine administered intravenously to dogs causes the hematocrit index to rise, probably because of contraction of the spleen.[1] A similar rise which occurs in traumatic shock is diminished by section of the spinal cord or spinal anesthesia. The relationship of these facts was brought to our attention because of the observation that the spleens of dogs which had died of traumatic shock were small and bloodless.

It seemed probable that sympathetic stimulation of the spleen might in part be responsible for the erythremia of traumatic shock in dogs. It has been attempted, therefore, to show that exclusion of the spleen by pharmacologic and surgical means reduces the anticipated increase in hematocrit index when shock is elicited by tourniquets or intestinal manipulation. Further, the question has been explored as to the importance of the spleen in the erythremia resulting from injections of epinephrine into normal and splenectomized human beings, on the assumption that epinephrine to some extent reproduces the blood picture which may be obtained in shock.

METHODS

All animals were anesthetized with pentobarbital sodium (30 mg. per kilogram of body weight administered intraperitoneally). Blood pressure was recorded with a mercury manometer and a kymograph connected to a cannulated carotid artery. Heparin solution and 10 per cent sodium citrate were used as anticoagulant. Six normal and 4 splenectomized dogs were each given 10 to 15 cc. of a $\frac{1}{10.000}$ solution of epinephrine hydrochloride intravenously over a period of sixty minutes. Splenectomy was done from one to seven days before the experiments were begun. Six normal human beings and 6 human beings whose spleens were removed after trauma or because of hemolytic jaundice were given 2 mg. of epinephrine hydrochloride in such a manner that the arterial pressure was maintained for forty-five to sixty minutes at 180 to 220 mm. of mercury systolic and 100 to 120 mm. of mercury diastolic. Thirty minutes before the epinephrine was administered, 0.4 Gm. of seconal sodium (sodium allyl-[methylpropylcarbonyl]-barbiturate) was given by mouth. This procedure was controlled by repeating the process in 6 normal persons with physiologic solution of sodium chloride substituted for the epinephrine solution.

Tourniquet shock was induced by applying four strands of ordinary package twine about the hindlimbs above the greater trochanter laterally and as high as possible medially. These were pulled tightly by hand so that partial venous and arterial occlusion resulted. The cords were cut at the end of four hours. Fifteen normal dogs, 12 splenectomized dogs and 6 dogs whose pressor response to epinephrine was reversed to depressor by intravenous injection of piperidomethyl-3-benzodioxane (Fourneau 933) were used. Reversal of the response to epinephrine was produced before giving the drug by infusing 8 to 10 cc. of solution containing 10 mg. of piperidomethyl-3-benzodioxane per cubic centimeter and was maintained for five to seven hours by a continuous drip of 6 to 8 drops per minute.

From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital.

1. (*a*) Barcroft, J., and Barcroft, H.: J. Physiol. **58**:138, 1923. (*b*) Cruickshank, E. W. H.: ibid. **61**:455, 1926. (*c*) Hargis, E. H., and Mann, F. C.: Am. J. Physiol. **75**:180, 1925. (*d*) de Boer, S., and Carroll, D. C.: J. Physiol. **59**:312 and 381, 1924. (*e*) Hanak, A., and Harkavy, J.: ibid. **59**:121, 1924.

To minimize the factor of loss of fluid into the injured areas, plaster casts were applied to the limbs with tourniquets on them. They were put on one hour before the experiment and extended to the level at which the cords had been applied. Six normal dogs, 4 splenectomized dogs and 4 dogs whose response to epinephrine had been reversed with intravenous injections of piperidomethyl-3-benzodioxane were used in these experiments.

Shock was produced in 10 normal dogs and 10 splenectomized dogs by gently manipulating the intestines for twenty-five minutes and leaving them exposed until death of the animal.

Hematocrit indexes were determined by the Wintrobe method with heparinized blood. Blood was drawn from the femoral artery in the dogs and from an antecubital vein without stasis in the human subjects.

RESULTS

1. Effect of Intravenously Administered Epinephrine in Normal and Splenectomized Dogs and Human Beings.—These results are illustrated graphically in chart 1 and tabulated in tables 1 and 2. One to 1.5 mg. of epinephrine hydrochloride given intravenously over a period of sixty minutes to 6 anesthetized

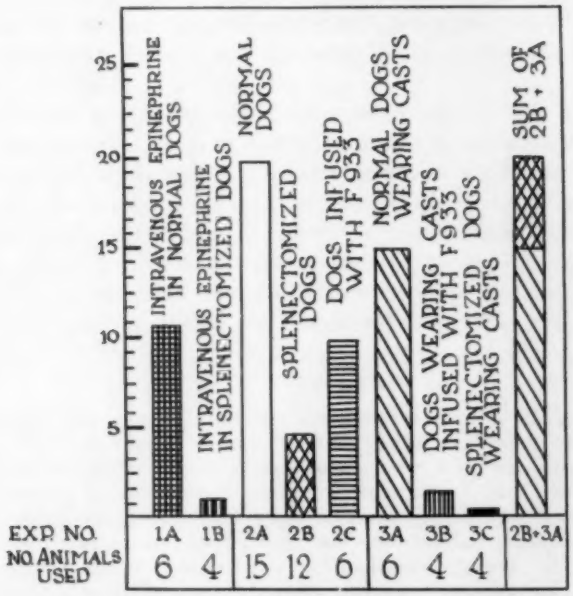

Chart 1.—Rise of hematocrit index observed in dogs after intravenous administration of epinephrine and during tourniquet shock in normal and splenectomized dogs and in dogs given an infusion of piperidomethyl-3-benzodioxane, both with and without casts.

normal dogs with an average hematocrit index of 38.5 mm. increased this average by 10.5 mm. (maximum 13 mm.; minimum 7 mm.). Further injections of epinephrine caused no greater rise in index. The same procedure carried out with 4 splenectomized dogs whose average hematocrit index was 34.4 mm. caused an average rise of 0.9 mm. (maximum 2 mm.; minimum 0.5 mm.) Thus the results sharply divided the splenectomized and nonsplenectomized animals.

Six normal human beings received 2 mg. of epinephrine hydrochloride intravenously at a rate rapid enough to maintain arterial blood pressure between 180 and 220 mm. of mercury systolic and 100 and 120 mm. of mercury diastolic for forty to sixty minutes (table 1). The average increase in hematocrit index in this group was 3.5 mm., which compares with a rise of 1.1 mm. in 6 splenectomized persons (table 2) subjected to the same procedure. The 6 normal control subjects

TABLE 1.—*Representative Experiments on Dogs and Patients Receiving Epinephrine Intravenously and Dogs Put into Shock with Tourniquets and by Intestinal Manipulation*

Experiment	Length of Experiment in Hours	Stage: Initial — Arterial Blood Pressure, Mm. Hg	Initial — Hematocrit Index, % of R. B. C.	Middle — Arterial Blood Pressure, Mm. Hg	Middle — Hematocrit Index, % of R. B. C.	Terminal — Arterial Blood Pressure, Mm. Hg	Terminal — Hematocrit Index, % of R. B. C.	Result
Intravenous injection of ephinephrine								
Normal dog	1.0	180	44	305	52.0	200	56.0	Lived
Splenectomized dog	1.0	145	31	200	32.0	200	33.0	Lived
Intravenous injection of ephinephrine								
Normal human being	1.0	102/60	40.5	180/ 90	44.1	160/80	43.7	Lived
Splenectomized human being	1.0	114/90	55.0	230-120	54.5	170/90	56.0	Lived
Tourniquet shock								
Normal dog	10.0	136	37.0	104	55.5	30	62.0	Died
Splenectomized dog	6.5	142	46.0	98	48.0	80	50.5	Died
Dog given infusion of piperidomethyl-3-benzodioxane	4.5	148	46.0	100	51.0	46	52.0	Died
Tourniquet shock of dogs wearing casts								
Normal dog	6.0	145	40.0	104	55.0	120	56.0	Lived
Splenectomized dog	9.5	138	52.0	108	54.5	128	53.0	Lived
Dog given infusion of piperidomethyl-3-benzodioxane	8.0	132	33.5	74	36.0	50	36.0	Lived
Intestinal stripping shock								
Normal dog	9.75	170	42.0	105	54.0	36	68.0	Died
Splenectomized dog	5.5	120	31.0	68	32.5	26	39.0	Died

TABLE 2.—*Changes in Hematocrit Index in Human Beings Following Intravenous Administration of Two Milligrams of Epinephrine*

Normal Subjects Given Physiologic Solution of Sodium Chloride: Patients and Diagnosis	Time, Minutes	Arterial Blood Pressure, Mm. Hg	Hematocrit Index, % of R. B. C.	Nonsplenectomized Patients: Patients and Diagnosis	Time, Minutes	Arterial Blood Pressure, Mm. Hg	Hematocrit Index, % of R. B. C.	Splenectomized Patients: Patients and Diagnosis	Time, Minutes	Arterial Blood Pressure, Mm. Hg	Hematocrit Index, % of R. B. C.
No. 1	0	110/70	44.0	No. 1, R. C.	0	132/86	38.0	No. 1	0	120/80	42.4
W. S.	15	104/70	43.4	carbon	5	240/120	38.5	W. R.	15	190/110	42.4
normal	30	110/70	44.5	tetra-	20	200/120	41.5	familial	30	190/110	43.0
	50	114/74	44.8	chloride	30	200/120	41.5	hemolytic	45	180/110	43.4
				poisoning				jaundice..	60	200/110	43.0
No. 2	0	108/62	48.0	No. 2, H. B.	0	102/60	40.5	No. 2, D. I.	0	114/90	55.0
R. T.	15	108/80	48.5	orthostatic	15	180/90	43.5	gunshot	15	230/120	55.5
normal	30	108/70	47.0	albumi-	35	190/100	44.2	wound of	30	215/110	56.0
	50	108/62	47.0	nuria	50	180/90	43.7	spleen	50	200/100	55.0
No. 3	0	108/70	39.0	No. 3	0	136/80	29.0	No. 3	0	136/80	46.0
E. B.	15	104/68	38.0	H. P.	15	216/100	32.5	M. K.	15	190/110	45.0
normal	30	104/70	38.0	secondary	30	190/90	31. 5	hemolytic	30	200/100	46.0
	50	108/68	38.0	anemia	50	196/100	30.5	anemia	50	180/100	46.0
No. 4	0	138/90	30.5	No. 4	0	116/70	30.5	No. 4, J. O.	0	136/70	48.0
L. F.	10	136/92	31.8	J. W.	15	170/100	32.5	gunshot	20	200/100	49.0
4 months	30	138/94	30.5	6 months	30	180/100	33.0	wound	30	190/96	48.0
pregnant	45	126/96	32.0	pregnant	50	160/90	34.0	of spleen	50	196/90	48.0
No. 5	0	124/60	32.5	No. 5	0	110/70	41.0	No. 5, S. J.	0	110/70	47.2
L. C.	10	126/70	32.0	M. D.	25	180/120	41.2	gunshot	20	200/110	48.2
normal	30	124/62	31.5	ovarian	45	190/120	42.0	wound	40	190/106	48.3
	40	124/64	32.0	cyst	55	186/130	43.0	of spleen	55	160/100	48.3
No. 6.	0	116/68	39.0	No. 6	0	116/80	34.0	No. 6, L. S.	0	130/190	49.0
J. J.	15	115/68	39.2	C. G.	20	180/118	34.6	thrombo-	15	180/110	48.8
normal	30	116/70	38.6	psycho-	45	190/122	37.0	cytopenic	30	160/120	48.0
	45	116/70	39.0	neurosis	55	180/126	38.0	purpura	50	126/70	50.0
Average increase			0.8				3.4				1.1

receiving physiologic solution of sodium chloride had an average rise in hematocrit index of 0.8 mm. Thus reasonable accuracy of the method was demonstrated.

2. Effect of Tourniquet Shock on Anesthetized Dogs, Splenectomized Dogs and Dogs Given an Infusion of Piperidomethyl-3-Benzodioxane.—Results of representative experiments of tourniquet shock induced in normal anesthetized dogs, splenectomized dogs and dogs given infusions of piperidomethyl-3-benzodioxane are presented in table 1. During the four hours the tourniquets were in place, swelling of the limbs and varying degrees of hypotension occurred. Occasionally an animal died in shock as early as two hours after application of cords. The arterial pressure fell to 80 to 90 mm. of mercury at the end of four hours in some animals, which maintained this level for six to eight hours and died eleven to fourteen hours after the beginning of the experiment. However, the usual picture consisted of a fall in blood pressure to 100 mm. of mercury during the period of vascular occlusion, followed by a precipitous fall of 20 to 40 mm. immediately following release of the constricting cords. This fall continued more slowly until the animal's death, after two to five hours. This average experiment was usually easily reproducible.

In 15 normal dogs the average hematocrit index was 40.8 mm. Tourniquet shock in these animals resulted in an average rise of 19.9 mm. from the beginning of the experiment to its ending by death (maximum 29 mm. and minimum 12 mm.). The same type of shock in 12 splenectomized dogs gave the less striking rise of 4.3 mm. from an initial index of 36.5 mm.

Six dogs receiving piperidomethyl-3-benzodioxane intravenously before induction of tourniquet shock exhibited an average increase in the index of 9.6 mm. (maximum 11.5 mm. and minimum 6.0 mm.) (chart 1).

Normal animals put into shock by the tourniquet method manifested 60 to 75 per cent of the total rise in the hematocrit index during the first hour of the experiment. Dogs given an infusion of piperidomethyl-3-benzodioxane had 40 to 50 per cent of the total rise in the index during the first one to two hours of the experiment. The remaining increase became evident gradually and evenly during the course of the experiments. In splenectomized animals no early sharp rise in the index was noted; the entire change was gradual. These findings point to a mechanism capable of delivering a large volume of red cells into the circulation. Piperidomethyl-3-benzodioxane, a sympathetic-paralyzing drug, partially inhibits this function, and splenectomy abolishes it, converting the changes into a gradually rising curve. Splenectomy did not, however, completely abolish hemoconcentration in animals shocked by the tourniquet method. The most obvious additional mechanism was local loss of plasma into the legs below the occluding tourniquets. To exclude this, plaster casts were applied to the hindlimbs and all experiments were repeated.

3. Effect of Tourniquet Shock on Anesthetized Normal Dogs, Splenectomized Dogs and Dogs Given an Infusion of Piperidomethyl-3-Benzodioxane, All of Which Wore Casts on Their Hindlimbs.—Results of tourniquet shock induced in normal anesthetized dogs, splenectomized dogs and dogs given an infusion of piperidomethyl-3-benzodioxane, all of which wore casts, are shown in chart 1, and representative experiments are recorded in table 2.

In this group of 14 dogs there was usually a gradual fall in arterial blood pressure from an average of 150 mm. of mercury to approximately 100 mm. of mercury during the first four hours. When the cords were released there was an abrupt but transient fall of 15 to 30 mm. of mercury. No further decline of pressure was noted. Fifty per cent of animals died forty-eight to ninety-six hours later with gangrenous changes in the legs, and the remaining animals survived.

The 6 control animals in this group showed an average rise in hematocrit index of 14.8 mm., 90 per cent of which occurred in the first quarter of the experiment (maximum 22 mm.; minimum 9 mm.), contrasting sharply with splenectomized dogs wearing casts, which experienced an average rise of 1.2 mm., and with 4 dogs with casts that were given an infusion of piperidomethyl-3-benzodioxane which had no rise.

4. Effect of Shock Induced by Intestinal Stripping of Anesthetized Normal and Splenectomized Dogs.—Representative experiments of this group are found in table 1. After twenty-five minutes of gentle manipulation of the intestines the arterial blood pressure fell from an average of 160 to approximately 110 mm. of mercury. This pressure was usually maintained for five to eight hours by the normal dogs and for three to five hours by the splenectomized dogs. The pressure then began to fall, reaching 60 to 80 mm. of mercury after one to two hours. Death usually occurred within the next two hours.

As with tourniquet shock, 50 per cent of the rise in the hematocrit index occurred during the first hour of the experiment. This immediate rise was not

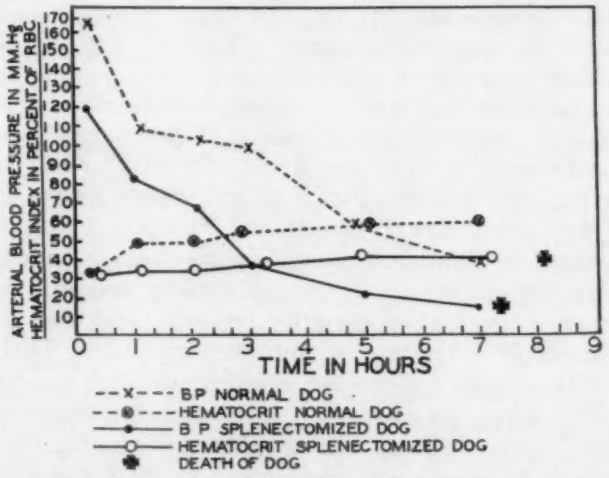

Chart 2.—Time relation of rise in hematocrit index for normal and for splenectomized dogs put into shock by intestinal manipulation.

noted in splenectomized dogs, in which all of the hemoconcentration developed gradually during the course of the experiment (chart 2).

Ten anesthetized normal dogs put into shock by intestinal stripping exhibited an average increase in hematocrit index of 26.0 mm. from an initial average index of 35.4 mm. (maximum 31 mm.; minimum 23.5 mm.), as compared with 10 splenectomized dogs under the same conditions, which showed an average increase of 13.4 mm. Thus 12.6 mm. is left to be accounted for by splenic participation.

REVIEW OF THE LITERATURE AND COMMENT

There is abundant evidence that the spleens of animals contract in response to various stimuli discharging highly cellular blood into the general circulation. In 1830 Dobson [2] first showed that the volume of dogs' spleens increased considerably following large feedings. He postulated that the spleen acted as a

2. Dobson, W.: An Experimental Inquiry into the Structure and Function of the Spleen, London, J. Wilson, 1830.

storage chamber for blood, thereby protecting the vascular system from sudden changes in blood volume, as during digestion. Wagner in 1849 [3] and Sabinski in 1865 [4] demonstrated contractibility of the canine spleen. This was shown to be of nervous origin by Schiff,[5] who elicited it in rabbits and cats by stimulating the splanchnic nerves and the semilunar ganglions. That nervous stimuli other than sympathetic could cause splenic contraction was shown in 1868 by Oehl,[6] who demonstrated it by stimulating the peripheral end of either vagus nerve in dogs, rabbits and cats. Tarchanoff [7] and Bulgak [8] caused splenic contraction by stimulation of the medulla. Roy [9] confirmed most of these observations in 1880 and added plethysmographic studies. He demonstrated rhythmic contractions normally present that varied considerably, increasing particularly during hypotension and with the appearance of Taube-Hering waves. He produced splenic contraction by stimulating either end of a cut sensory nerve. Schäfer and Moore [10] found the spleens of dogs responsive to changes in blood pressure and to asphyxia and epinephrine. They studied the nerve supply of the spleen and found it received both motor and inhibitory fibers through the splanchnic nerves. The motor fibers arose from the third thoracic to the first lumbar but chiefly from the fifth to the tenth thoracic segment. Hargis and Mann [1c] studied changes in volume of canine spleens with the plethysmograph. They used food, excitement and epinephrine as stimuli to prove that splenic contraction was due to a vasomotor mechanism which could be abolished by splenic denervation. The intrasplenic pressure produced by contraction was measured by Richberg,[11] who tied off the blood supply to and from the organ and found an average rise of 70 to 80 mm. of mercury following electrical stimulation of the splenic nerves.

Barcroft and his co-workers,[12] Hanak and Harkavy,[1e] Cruickshank [1b] and others [13] have gathered evidence that the spleen contracts in response to carbon monoxide poisoning, hemorrhage, exercise, rebreathing and injection of an epinephrine solution or of solution of posterior pituitary, and that this contraction discharges an extra supply of erythrocytes into the circulation. Their studies were conducted in the main on dogs and cats but included rabbits, horses and monkeys.

Contraction of the spleen is apparently a well established vasomotor mechanism responding to varied stimuli. There is also evidence indicating that such activity delivers highly cellular blood into the circulation. In 1908 Boveri [14] and in 1912

3. Wagner, R.: Ueber die Contractilität der Milz, Nachr. v. d. k. Gesellsch. d. Wissensch. u. d. Georg.-Aug. Univ. Göttingen. **2**: 89, 1849.

4. Sabinski, Z.: Sudebno med. znachenie pjaten Tardieu pri smerti ot zadushenija (suffocatio) i anemii selezenki pri asphiktich-eskich smertjach, Thesis, St. Petersburg, 1865.

5. Schiff, J. M.: Leçons sur la physiologie de la digestion, faites au Muséum d'histoire naturelle de Florence. Redigées par Émile Levier, Florence, H. Loescher, 1867.

6. Oehl, E.: Gazz. med. ital. lomb. **1**:10, 1868.

7. von Tarchanoff, F.: Arch. f. d. ges. Physiol. **8**:97, 1874.

8. Bulgak, J.: Virchows Arch. f. path. Anat. **69**:181, 1877.

9. Roy, C. S.: J. Physiol. **3**:203, 1880.

10. Schäfer, E. A., and Moore, B.: J. Physiol. **20**:1, 1896.

11. Richberg, E.: Ztschr. f. Biol. **89**:481, 1930.

12. (*a*) Barcroft, J.; Murray, C. D.; Arahovats, D.; Sands, J., and Weiss, R.: J. Physiol. **60**:443, 1925. (*b*) Barcroft, J.: Lancet **1**:544, 1926. (*c*) Barcroft, J., and Poole, L. T.: J. Physiol. **64**:23, 1928. (*d*) Barcroft, J., and Stephens, J. G.: ibid. **64**:1, 1928.

13. Binet, L., and Williamson, R.: Scandinav. Arch. f. Physiol. **49**:92, 1926. Binet, L.; Cardot, H., and Williamson, R.: Compt. rend. Soc. de biol. **95**:262, 1926. Binet, L., and Fournier, B.: ibid. **95**:1141, 1926. Viale, G., and di Leo Lira, J.: ibid. **97**:1239, 1926. Müller, H. K.: Ztschr. f. Biol. **87**:307, 1928. Abderhalden, E., and Roske, A.: Arch. f. d. ges. Physiol. **216**:308, 1927. de Boer and Carroll.[1d, e]

14. Boveri, P.: Biophysikal. Centralbl. **3**:511, 1907-1908.

Steiger [15] reported polycythemia in dogs following injection of epinephrine. Lamson [16] reported a 25 to 39 per cent increase in red blood cell counts of cats following excitement, a response prevented by adrenalectomy. Izquierdo and Cannon [17] in 1928 confirmed the occurrence of emotional polycythemia in cats and prevented it by splenic denervation.

Barcroft and Poole [12c] added a valuable link to this chain of evidence indicating that splenic contraction results in the polycythemia found after epinephrine, excitement, anoxia and food by experiments showing splenic blood to be at least 50 per cent richer in hemoglobin than peripheral blood. This work supported similar reports of Cruickshank [1b] and Scheunert and Krzywanek.[18]

Kendrick and Uihlein [19] applied this principle to dogs in shock. Their animals were anesthetized with ether and put into shock by intestinal manipulation. Midway in the experiment ether anesthesia was replaced by use of sodium pentobarbital. The nonsplenectomized dogs had a decrease in hematocrit index, presumably due to splenic relaxation. The change of anesthetic for splenectomized animals produced no such difference. Hausner, Essex and Mann [20] outlined the spleen with pellets of lead by the method of Barcroft and Harris. They observed contraction in animals under ether anesthesia that resulted in polycythemia. When sodium pentobarbital was substituted for ether anesthesia the spleen was seen to relax, with a resulting decided reduction of the red blood cells in the peripheral blood.

This body of evidence was doubted by Hahn, Bale and Bonner,[21] who used radioactive iron to study red blood cell mass (volume of circulating red blood cells). They found no increase in red cell mass after injecting epinephrine intravenously into normal anesthetized dogs and concluded that the rise in hematocrit index could not be due to discharge of red cells previously stored in the spleen. However, they, as have others, found that splenectomy abolished the increase in hematocrit index following injection of epinephrine. This being true, their results might be questioned.

As regards splenic participation in the hemoconcentration of shock, Keeley, Gibson, and Pijoan [22] found that splenectomy abolished it in burn shock. Searles and Essex [23] and Essex, Seeley, Higgins and Mann [24] demonstrated that anesthesia induced with barbiturates caused hemodilution due to splenic relaxation with consequent removal from free circulation of large volumes of red cells. Moon [25] described contraction of the spleen in shock. Lewis, Werle and Wiggers [26] exteriorized the spleen and measured the decrease of volume in dogs put into shock by bleeding.

15. Steiger, O.: Med. Klin. **8**:1746, 1912.
16. Lamson, P. D.: J. Pharmacol. & Exper. Therap. **7**:169, 1915; **9**:129, 1916; **16**:125, 1920.
17. Izquierdo, J. J., and Cannon, W. B.: Am. J. Physiol. **84**:545, 1928.
18. Scheunert, A., and Krzywanek, F. W.: Arch. f. d. ges. Physiol. **213**:198, 1926.
19. Kendrick, D. B., Jr., and Uihlein, A.: Surgery **12**:76, 1942.
20. Hausner, E.; Essex, H. E., and Mann, F. C.: Am. J. Physiol. **121**:387, 1938.
21. Hahn, P. F.; Bale, W. F., and Bonner, J. F., Jr.: Am. J. Physiol. **137**:717, 1942.
22. Keeley, J. L.; Gibson, J. G., Jr., and Pijoan, M.: Surgery **5**:872, 1939.
23. Searles, P. W., and Essex, H. E.: Proc. Staff Meet., Mayo Clin. **11**:481, 1936.
24. Essex, H. E.; Seeley, S. F.; Higgins, G. M., and Mann, F. C.: Proc. Soc. Exper. Biol. & Med. **35**:154, 1936.
25. Moon, V. H.: Shock and Related Capillary Phenomena, New York, Oxford University Press, 1938.
26. Lewis, R. N.; Werle, J. M., and Wiggers, C. J.: Am. J. Physiol. **138**:205, 1943.

Mylon, Winternitz, Katzenstein and de Süto-Nagy [27] found that section of the spinal cord of dogs greatly reduced the hemoconcentration seen in shock induced by arterial occlusion of hindlimbs for five and one-half hours. They concluded:

> . . . that any influence . . . that allows the parasympathetic nervous system to dominate results in low blood pressure and increased permeation of fluid and protein through the capillary wall. . . . The gradual fall in blood pressure that follows release of the arterial occluding tourniquet is not influenced by section of the spinal cord. On the other hand, the increase in red cell volume and loss in plasma protein is eliminated by this procedure.

They attribute the absence of hemoconcentration to interruption of the parasympathetic nervous system. However, we assumed that since the vagi were intact in their animals, the phenomenon must be due to inhibition of sympathetic motor impulses to the spleen, these being interrupted by section of the spinal cord.

The belief that the spleen plays a role in the hemoconcentration of tourniquet shock is supported by our finding that surgical removal reduced the average increase in hematocrit index in shock from 19.9 in normal animals to 4.33 mm. in splenectomized animals, and in shock following intestinal manipulation from 26.0 mm. in normal dogs to 13.4 mm. in splenectomized subjects. When the sympathetic-paralyzing drug piperidomethyl-3-benzodioxane reversed the pressor response to epinephrine to a depressor response, we observed an average increase in hematocrit index of only 9.6 mm. in tourniquet shock, as compared with 19.9 mm. in dogs receiving none of the drug.

It seems reasonable that "pharmacologic splenectomy" should be less complete than surgical extirpation. That this is true is shown by the fact that a rise of 9.6 mm. occurred in hematocrit index after infusion of piperidomethyl-3-benzodioxane, as compared with 4.33 after splenectomy. Both of these procedures abolished the rise usually seen in the first quarter of the experiment.

Casts have been applied to reduce loss of fluid into the injured limbs, a procedure also used by Katz, Shleser, Asher and Perlow [28] before ligating the common iliac vein. In the normal dogs, after application of tourniquets the rise in hematocrit index was only 14.8, as compared with the anticipated 19.9 mm. On the contrary, splenectomy and administration of piperidomethyl-3-benzodioxane along with casts completely abolished hemoconcentration. The sum of the increase in index in splenectomized dogs and normal dogs wearing casts is 19.1 mm., which is comparable to the 19.9 mm. increase in normal animals with tourniquet shock. This evidence suggests that local loss of fluid and contraction of the spleen account for the hemoconcentration seen in tourniquet shock in dogs.

In shock induced by loss of plasma from intestinal stripping and exposure, splenectomized animals exhibited an average rise in hematocrit index 12.6 mm. less than that of normal animals. This type of shock, due primarily to loss of plasma, resulted in a greater degree of hemoconcentration than is seen in animals with tourniquet shock. However, the spleen contributed approximately the same degree of increase in the index (12.6 mm., as compared with 14.8 mm.).

These observations suggesting that the hemoconcentration of tourniquet shock is due to splenic contraction and local loss of fluid are not supported by the studies of Cullen, Schechter, Freeman and Laws.[29] These authors used the

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27. Mylon, F.; Winternitz, M. C.; Katzenstein, R., and de Süto-Nagy, G. J.: Am. J. Physiol. **137**:280, 1942.

28. Katz, L. N.; Shleser, I. H.; Asher, R., and Perlow, S.: Am. J. Physiol. **137**:589, 1942.

29. Cullen, M. L.; Schecter, A. E.; Freeman, N. E., and Laws, M. K.: Blood Substitutes and Blood Transfusion, Springfield, Ill., Charles C Thomas, Publisher, 1942, vol. 5.

carbon monoxide method to determine changes in blood volume in traumatic shock following 1,500 blows of a rubber mallet to a limb, and they found the reduction in blood volume greater than could be accounted for by the measured loss into the injured legs in both normal and sympathectomized dogs. However, the determination of blood volume by this method depends on the degree of saturation of the red blood cells with carbon monoxide. Barcroft and Barcroft [1a] and Hanak and Harkavy [1e] showed that animals at rest could breathe for two hours concentrations of carbon monoxide sufficient to raise the carboxyhemoglobin in the peripheral blood to 20 per cent without its appearing in splenic blood. Splenic discharge of many erythrocytes could give evidence of apparent loss of fluid in the normal subjects. The same mechanism to a lesser degree might be noted in the sympathectomized animals, since slower and less pronounced splenic contraction was observed by Hargis and Mann [1c] after sympathectomy. Neither section of the spinal cord [27] nor administration of the sympathetic-paralyzing drug piperidomethyl-3-benzodioxane in our experiments completely abolished the contribution of the spleen to the change in hematocrit index in tourniquet shock.

It is suggested that the spleen causes the rise in hematocrit index seen in dogs after injection of epinephrine and during the early stage of traumatic shock due to constriction of the dog's limbs or following intestinal stripping. Since the whole of the hemoconcentration in our animals can be accounted for by loss of fluid into the damaged limb and by splenic contraction, the concepts that generalized increased capillary permeability or systemic sequestration of plasma occurs in shock are not supported.

The question at once arises whether the spleen behaves similarly in man. In 1852 Henle [30] observed splenic contraction in human beings after decapitation. Paffenholz and Schürmeyer [31] and Volicer and Vesin [32] used colloidal thorium dioxide to visualize slight but definite contraction of the spleen after injection of epinephrine. If the spleen is enlarged, however, great contraction may occur (Watson [33]).

The first suggestion that emotional polycythemia may occur in either human beings or animals was derived from experiments conducted on medical students in 1897. Ferrari [34] counted the red blood cells of a group of young men before and after an examination and found the average rise to have been 457,000 cells per cubic millimeter. Ebert and Stead [35] concluded that the large increases in blood volume following injection of epinephrine and exercise reported by Barcroft,[36] Bazett [37] and others [38] could be accounted for by inaccuracy of the carbon monoxide and dye methods of measuring blood volume. They, as well as Lucia, Aggeler, Husser and Leonard,[39] were unable to differentiate normal from splenectomized persons by changes in the hematocrit index following subcutaneous admin-

30. Henle, F. G. J.: Ztschr. f. rat. Med. **2**:229, 1852.
31. Paffenholz, W., and Schürmeyer, A.: Klin. Wchnschr. **10**:2076, 1931.
32. Volicer, L., and Vesin, S.: Ztschr. f. klin. Med. **122**:57, 1932.
33. Watson, C. J.: Ann. Int. Med. **12**:1782, 1939.
34. Ferrari, G. C.: Riv. di pat. nerv. **2**:306, 1897.
35. Ebert, R. V., and Stead, E. A.: Am. J. M. Sc. **201**:655, 1941.
36. Barcroft, J.; Binger, A.; Bock, A. V.; Daggart, J. H.; Forbes, H. S.; Harrop, G.; Meakins, J. C., and Redfield, A. C.: Phil. Tr. Roy. Soc., London, s.B **211**:419, 1922.
37. Bazett, H. C.; Sunderman, F. W.; Doupe, J., and Scott, J. C.: Am. J. Physiol. **129**:69, 1940.
38. Ludwig, H.: Ztschr. f. d. ges. exper. Med. **80**:36, 1931. Wollheim, E.: Ztschr. f. klin. Med. **116**:269, 1931.
39. Lucia, S. P.; Aggeler, P. M.; Husser, G. D., and Leonard, M. D.: Proc. Soc. Exper. Biol. & Med. **36**:582, 1937.

istration of 1 mg. of epinephrine hydrochloride. Nor could Dill, Talbott and Edwards [40] find any difference among normal and splenectomized persons following exercise.

In our 6 normal subjects there was an average rise in hematocrit index of 3.4 mm., as compared with a 1.1 mm. change in splenectomized subjects, after intravenous injection of 2 mg. of epinephrine hydrochloride. This is small compared with the 10.5 mm. change seen in our dogs, but it is constant and probably of some significance. The fact that a rise occurred in our experiments and not in others is doubtless due to the use of 2 mg. of epinephrine hydrochloride intravenously as compared with 1 mg. subcutaneously.

On the basis of this evidence it seems that the human spleen contributes much less to the rise in hematocrit index seen in shock than do the spleens of dogs. However, final judgment must be reserved until more is known of human splenic blood volume, and whether the spleen contains highly cellular blood and whether it contracts actively.[41]

SUMMARY AND CONCLUSIONS

Approximately 65 per cent of the rise in hematocrit index in dogs in tourniquet shock and 50 per cent of that in shock induced by intestinal manipulation can be accounted for by splenic contraction and discharge of highly cellular blood from the spleen.

The splenic contribution to changes in the hematocrit index occurs during the first one to two hours of the experiment.

This portion of erythremia can be eliminated by splenectomy and partially so by infusion of piperidomethyl-3-benzodioxane. Both procedures prevent the early, sharp rise of the hematocrit index seen in traumatic shock.

Thirty-five per cent of the rise in hematocrit index in tourniquet shock can be prevented by applying plaster casts to the hindlimbs. Practically all increase can be eliminated with casts applied to the traumatized limbs combined with either infusion of piperidomethyl-3-benzodioxane or splenectomy.

Since hemoconcentration in the types of shock under investigation can be accounted for by local loss of plasma at the site of injury and splenic participation, the concept of generalized increase in capillary permeability is not supported.

Epinephrine produced a slight rise in the hematocrit index in 6 normal persons but not in 6 splenectomized persons. The rise was one third of that seen in dogs. It appears that splenic participation may not be as significant in traumatic shock of human beings as in that of animals.

Indianapolis City Hospital.
960 Locke Street.

40. Dill, D. B.; Talbott, J. H., and Edwards, H. T.: J. Physiol. **69**:267, 1930.

41. Since this manuscript was submitted, C. J. Watson and J. R. Paine (Am. J. M. Sc. **205**:493, 1943) have reported observations made on 9 patients during splenectomy. They found that epinephrine caused marked splenic contraction and an associated systemic erythremia due to discharge of cellular splenic blood. This report obviates the need for studies we had in progress.

ANGIOFIBROMA OF THE ILEUM

CLINICAL PICTURE IN TUMORS OF THE SMALL INTESTINE

MANUEL E. LICHTENSTEIN, M.D.
AND
FRANK R. DUTRA, M.D.
CHICAGO

Benign tumors of the small intestine are not common (tables 1 and 2). They are seldom recognized before operation or autopsy.

Since the first comprehensive review of benign tumors of the small intestine was published in 1899 by Hertaux,[1] there have been few extensive contributions to the subject. In 1917, King [2] compiled abstracts of 118 cases of benign tumor recorded in the literature and gave a complete report of 1 case of sessile submucous

TABLE 1.—*Comparative Incidence of Tumors of the Stomach, Small Intestine and Large Intestine*

Author	Material	Location	Benign	Malignant	Total
Raiford [4]	Autopsies, 11,500	Stomach	56	453	511
		Small intestine	33	38	71
	Surgical specimens, 45,000	Colon	87	281	368
			178	772	950
Merchant [8]	Autopsies, 7,340	Stomach	43		
		Small intestine	24		
	Surgical specimens, 50,775	Colon	177		
			244		

TABLE 2.—*Comparative Incidence of Benign and Malignant Tumors of the Small Intestine*

Author	Benign	Malignant	Total
Raiford [4]	33	38	71
Hartman [*]	44	97	141

[*] Hartman, H. R.: Lesions of Small Bowel Other Than Peptic Ulcer, M. Clin. North America **19**: 365, 1935.

fibroma of the jejunum. Brown,[3] in 1924, reported an instance of cavernous hemangioma of the jejunum and reviewed the literature on vascular tumors of the intestines. In 1932, Raiford [4] published a thorough discussion of tumors of the small intestine. He found 33 benign tumors of the small intestine [5] described in all available records at the Johns Hopkins Hospital; the material reviewed included 11,500 general autopsies and 45,000 general surgical specimens. The complete records of the Mayo Clinic up to 1933 were reviewed by Rankin and

From the Departments of Surgery and Pathology, Northwestern University Medical School, and the Norwegian-American Hospital.

1. Hertaux: Note sur les tumeurs benignes de l'intestin, Arch. prov. de chir. **8**:701, 1899; **9**:1, 1900.
2. King, E. L.: Benign Tumors of the Intestine, Surg., Gynec. & Obst. **25**:54, 1917.
3. Brown, A. J.: Vascular Tumors of the Intestine, Surg., Gynec. & Obst. **39**:191, 1924.
4. Raiford, T. S.: Tumors of the Small Intestine, Arch. Surg. **25**:122 (July) 1932.
5. This figure does not include carcinoids, ectopic pancreatic tissue and cysts.

Newell.[6] They summarized 35 cases of benign tumor of the small intestine, 11 of which had been previously reported. Kirshbaum [7] reviewed the 5,754 autopsies at the Cook County Hospital from 1929 to 1935 and found 12 cases of benign tumor of the small intestine. Merchant [8] summarized the records of the Royal Victoria Hospital of Montreal from 1915 to 1939 and found 6 benign tumors among 50,775 surgical specimens and 18 reported in 7,340 autopsies. The greater incidence of these tumors in autopsy material as contrasted with surgical material is due in part to the fact that some are undiagnosed clinically and in part to the fact that many are merely observed incidentally at autopsy.

There have been other reports of single cases in which no unusual features were presented.

A benign tumor of the small intestine may arise from any of the components of the wall. Table 3 gives a summary of the place of occurrence and the nature of the tumors reported by several authors. It shows that they were more frequent in the ileum than in the jejunum or duodenum. Of interest is the occurrence of neurofibroma as indicated by Grill and Kuzma,[9] either with or without von Recklinghausen's neurofibromatosis. There have been 5 cases of nerve sheath tumor (neurilemmoma) of the small intestine reported,[10] in 2 of which the growth

TABLE 3.—*Location and Character of Benign Tumors of the Small Intestine* *

Type	Duodenum	Jejunum	Ileum	Unspecified	Total
Fibroma	2	4	10	1	17
Fibroadenoma	1	..	..	..	1
Myoma and fibromyoma	8	10	15	4	37
Adenoma	10	8	14	..	32
Angioma	3	2	1	1	7
Lipoma	4	2	7	4	17
Neurofibroma	1	..	..	3	4
Osteochondroma	..	..	..	1	1
Total	29	26	47	14	116

* Compiled from papers by King,[2] Ralford,[4] and Rankin and Newell.[6]

was in the duodenum and in 3 in the jejunum or ileum. This type of tumor is encountered in the stomach much more frequently than in the intestine. Rarely, a congenital lesion is found, such as the hemangioendothelioma in the case reported by Blahd, Maschke and Karsner.[11]

The direction of enlargement of a tumor depends on whether it arises on the luminal side or on the extraluminal side of the muscular layer. Thus, a fibroma arising in the submucosa projects into the lumen of the canal, while one in the subserosa projects into the peritoneal cavity. A myoma which arises from the muscular layer may project in either direction.

6. Rankin, F. W., and Newell, C. E.: Benign Tumors of the Small Intestine: Report of Twenty-Four Cases, Surg., Gynec. & Obst. **57**:501, 1933.

7. Kirshbaum, J. D.: Submucous Lipomas of the Intestinal Tract as a Cause of Intestinal Obstruction, Ann. Surg. **101**:734, 1935.

8. Merchant, F. T.: Intussusception Due to Hemangioma of the Jejunum, Arch. Surg. **39**:1031 (Dec.) 1939.

9. Grill, J., and Kuzma, J. F.: Recklinghausen's Disease with Unusual Symptoms from Intestinal Neurofibroma, Arch. Path. **34**:902 (Nov.) 1942.

10. Stout, A. P.: The Peripheral Manifestations of the Specific Nerve Sheath Tumor (Neurilemoma), Am. J. Cancer **24**:751, 1935.

11. Blahd, M. E.; Maschke, A. S., and Karsner, H. T.: A Case of Hemangio-Endothelioma of the Ileum, Am. J. Dis. Child. **26**:379 (Oct.) 1923.

The development of the extraluminal type of tumor is insignificant when contrasted with that of the intraluminal type. As the latter projects into the lumen, it may be sessile at first. In most instances the peristaltic activity exerts sufficient force to move the mass away from its point of origin, so that a pedicle is formed. With pedunculated tumors, complications are much more frequent than with other forms.

There are four complications which may occur with a pedunculated tumor of the small intestine: (1) necrosis of the tumor mass; (2) bleeding from an eroded surface; (3) partial or complete obstruction of the lumen, and (4) intussusception. These may coexist in the same person. Necrosis occurs because of paucity of circulation through an attenuated pedicle. Fever and persistent occult blood in the stools may result from necrosis or from erosion. Partial obstruction due to a tumor is identical with that from any other cause. There are hypertrophy of the tunica muscularis and dilatation of the lumen above the obstruction, while below it the intestinal wall is unchanged and the lumen small. Complete obstruction results from intussusception of the tumor-bearing segment into the subadjacent portion of bowel or may be due to encroachment of the tumor on the lumen or impaction of intestinal contents against it. In this condition, the lumen above the obstruction is dilated and the walls are thin and tense.

Chronic, intermittent or acute intestinal obstruction is suggested by the history. Recurrent attacks of acute abdominal pain with intervals free from pain are common. The attacks of pain tend to become more severe with each recurrence. Nausea and vomiting are frequent during the attacks, being intense if the tumor is high in the small intestine.

The intermittent colicky pain repeatedly starts in the same area and tends to remain localized. Owing to the frequent location of the tumor in the ileum, the pain is often in the right lower quadrant of the abdomen; hence, differentiation from appendicitis is necessary. These attacks of pain associated with nausea and often with vomiting end suddenly, and the patient feels well until the next attack.

Constipation is a frequent complaint. It is usually marked between the episodes of obstruction and complete during them.

Physical symptoms are few if there are no complications. There may be evidence of a recent loss of weight; this is more often apparent with a malignant tumor. As with other forms of mechanical obstruction, there is often a region of localized tenderness in the abdomen, and sometimes a mass can be palpated.

Examination of the stools sometimes reveals frank or occult blood. This is especially frequent if the growth is a cavernous hemangioma. Any type of benign tumor in the duodenum is likely to produce considerable hemorrhage. Balfour and Henderson [12] emphasized this in a review of 6 benign tumors of the duodenum (2 myomas, 2 adenomas, 1 adenomatous polyp and 1 hemangioma). They stated: "The most significant sign was hemorrhage, which was severe in 4 of the 6 cases."

After one or more of the attacks of obstruction, a symptom-free interval may be ended by acute intussusception. There is a sudden onset of severe pain, and it is localized to a definite area. Palpation frequently reveals an elongated sausage-shaped abdominal mass. Vomiting and abdominal distention occur, and bloody stools may be passed.

12. Balfour, D. C., and Henderson, E. F.: Benign Tumors of the Duodenum, Ann. Surg. **89**:30, 1929.

The use of the roentgen rays in the diagnosis of tumors of the small intestine is seldom discussed in the literature. Kiefer [13] stated that the roentgen examination may be disappointing except when carried out either during or just after a period of obstruction. At such a time, a flat plate roentgenogram may reveal the distended loops of small intestine in "stepladder" arrangement. Fluid levels may be present in the distended loops. The administration of barium sulfate by mouth is contraindicated in the presence of acute intestinal obstruction; when there has been chronic obstruction or repeated episodes of complete obstruction have occurred, it should be used only with full realization that it can precipitate acute obstruction.

REPORT OF A CASE

A 68 year old white woman was admitted to the Norwegian-American Hospital on April 8, 1940, complaining of vague intermittent abdominal cramps of four months' duration. These had often been associated with attacks of nausea in the preceding two months. For three

Fig. 1.—Roentgenogram taken after a barium sulfate meal. The arrow indicates the filling defect interpreted as a probable tumor of the ileum.

weeks there had been occasional vomiting accompanying the cramps and nausea. Blood had not been noted in the vomitus, nor had the stools been tarry. She had had a poor appetite and had been constipated since the onset of symptoms. Before her admission to the hospital, she had had a barium sulfate meal. This revealed a filling defect in the ileum, which was interpreted as probable tumor of the small intestine (fig. 1).

The patient was an elderly, well developed, fairly well nourished woman who was not acutely ill. The blood pressure was 168 systolic and 94 diastolic; the pulse rate was 88 and the respiratory rate 24 per minute, and the temperature was 99.4 F. The abdomen was distended; no organs or masses were palpable, but there was slight tenderness on the right side of the umbilicus. There were no other unusual findings. The erythrocyte count was 3,600,000, the hemoglobin content 12 Gm. and the leukocyte count 9,700. The urine contained albumin (3 plus) and occasional casts. The report on a flat plate roentgenogram of the abdomen was "considerable gas throughout the upper portion of the small intestine."

It was believed that there was obstruction of the small intestine, and preparations for operation were instituted. These consisted of hydration and the supplying of iron, minerals and

13. Kiefer, E. D.: Clinical Aspects of Chronic Disorders of the Small Intestine, J. A. M. A. **113**:1546 (Oct. 21) 1939.

Fig. 2.—Pedunculated angiofibroma of the ileum. The intussusceptions were reduced before the resection was done.

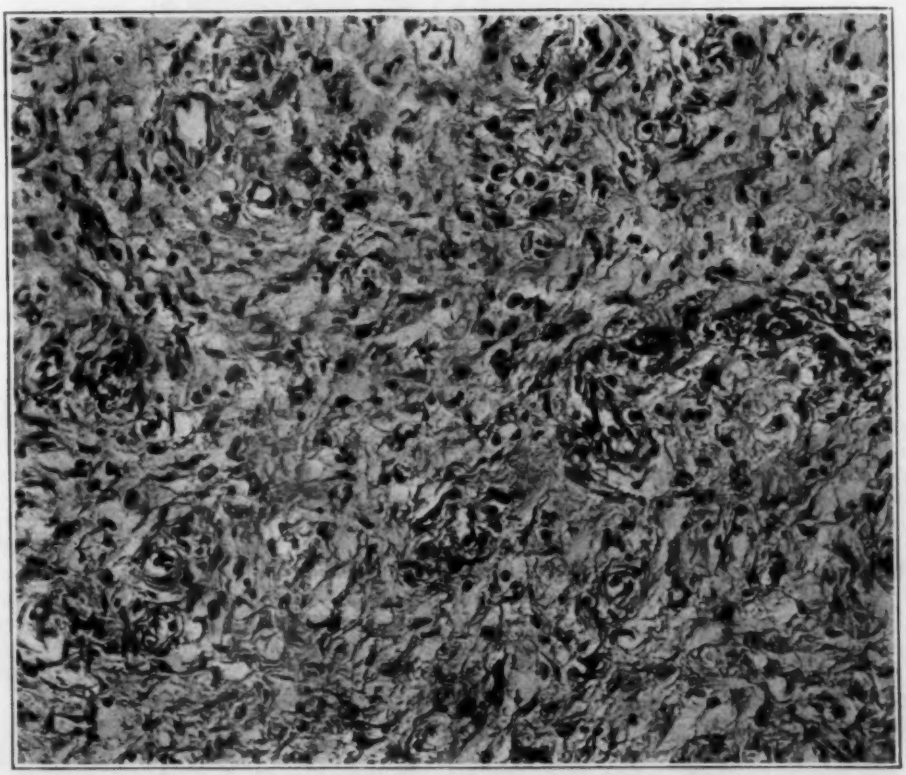

Fig. 3.—Angiofibroma of the ileum (× 100). There are numerous vascular spaces lined by flat endothelial cells.

vitamins. A high caloric liquid diet was allowed. Intermittent intestinal suction, with use of a Miller-Abbot tube, was also employed, in order to secure and maintain decompression of the intestine above the obstruction. During this period of preparation, the temperature reached 99.4 F. on several occasions.

On April 13, the abdomen was opened, and a double intussusception was found in the ileum. This was an invaginated section of ileum with a pedunculated tumor near its tip, and the entire intussusception and tumor had subsequently invaginated into the next lower segment of ileum (fig. 2). The lumen above the obstruction was dilated and the wall thickened. The intussusceptions were reduced, and 8 cm. of intestine, including the tumor, was resected. Primary end to end anastomosis was done. The convalescence was uneventful, and the patient was discharged on the eleventh postoperative day. After the third postoperative day, the temperature did not rise above 98.6 F.

Pathologic Report (Dr. H. R. Fishback).—Gross Observations: The specimen consisted of a segment of bowel 7 cm. in length, the wall of which appeared unchanged. Near one end of the segment there projected from the mucosa into the lumen a pedunculated tumor mass 4 cm. in length and 2.5 cm. in diameter. The proximal end of this was grayish pink and had a smooth mucosal covering. The distal half was dark bluish red and had an eroded surface. On section the tissue had a central pinkish white fibrous core. Around this, beneath the covering of the mucosa, was a slightly softer zone 5 mm. thick, which was pinkish yellow.

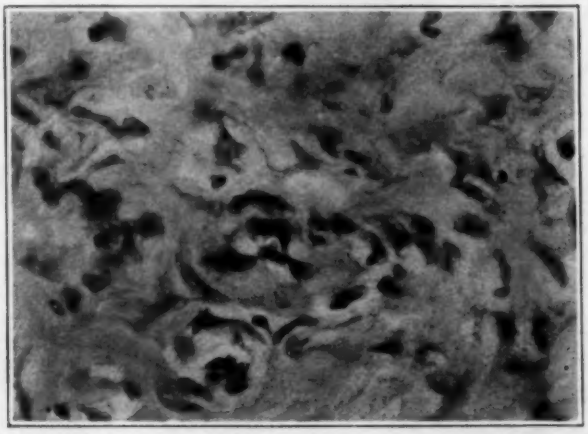

Fig. 4.—Angiofibroma of the ileum (× 200). The vascular spaces are surrounded by fibroblasts and strands of collagen.

Microscopic Observations (figs. 3 and 4): Sections showed a structure made up of white fibrous connective tissue. This was intimately interlaced between innumerable small capillary blood vessels. In places these had well defined walls, but in others the walls were largely endothelial cells and many of the capillaries appeared collapsed. Here and there were diffuse small streaks of hyalinization. Part of the tumor was covered over by intestinal mucosa, somewhat engorged and containing inflammatory cells, and it showed a layer of muscularis mucosae. A portion was ulcerated, with a covering of fibrin mingled with red cells and leukocytes. Beneath this was an area of chronic inflammatory reaction of nonspecific type.

Diagnosis: The diagnosis was angiofibroma of the intestine.

Subsequent Course.—Fourteen months after the operation, a report was received from the patient's daughter in which it was stated that within four months after the removal of this tumor there had been a gain of weight of 24 pounds (11 Kg.). The patient had had a good appetite, and there had been no further constipation.

COMMENT

Double intussusception resulting from a tumor of the small intestine was reported by James Nicoll in 1899. This was in a woman of 23 years who was seen with pain, persistent vomiting and constipation. She had had a similar attack two weeks before, but it had been milder; in the intervening two weeks

pain after meals had been frequent, lasting about an hour each time. At operation, a double intussusception was found. A portion of intestine 5 feet (1.5 meters) long was resected, and in the lumen, "just above the intussusception, was a tumor about the size of a pigeon's egg." End to end anastomosis was done, and the patient recovered. The tumor was a typical cavernous hemangioma.

Vague, intermittent abdominal cramps, sometimes associated with nausea and vomiting, should lead to consideration of partial obstruction of the intestine. Constipation of marked degree is also a part of this picture. When such a history is climaxed by an acute intussusception (signs of complete obstruction plus a palpable abdominal mass), the presence of a pedunculated tumor of the small intestine is highly probable.

The sequence of intestinal obstruction followed by a symptom-free period recurring at variable intervals results from local spasm of the intestine in the vicinity of the tumor or from partial invagination. Sudden relief follows relaxation of the former or reduction of the latter.

Anemia in this patient was due to her diminished appetite and limited retention of food resulting from the chronic partial intestinal obstruction. These factors also explain her constipation. The low grade fever occasionally present before operation may be explained by the presence of necrosis at the tip of the tumor, from which protein products could enter the blood stream. After the operation this fever did not recur. Albuminuria was caused by an unrelated chronic glomerulonephritis.

The complete absence of symptoms for fourteen months after the operation attests the importance of diagnosis and surgical therapy for benign tumors of the small intestine.

The microscopic structure of this tumor was one of many capillary vessels and capillary buds in a bed of fibrous connective tissue. Many of the vessels were merely endothelium-lined spaces surrounded by connective tissue, without other evidence of a wall. This structure closely fits the characteristic picture of angiofibroma as described by Ewing.[14] Angiofibroma may arise from the vascular elements of any part of the body; although growths of this type have been reported in many organs, none has been reported previously in the small intestine.

SUMMARY

The literature on benign tumors of the small intestine is briefly reviewed.

There are two directions in which such a tumor may expand: toward the peritoneal cavity (extraluminal) and toward the lumen of the intestine (intraluminal). Growth in the former direction rarely results in complications, while intraluminal expansion is frequently associated with necrosis, bleeding, intestinal obstruction and intussusception.

Diagnosis is made from a history of recurrent attacks of colicky pain associated with nausea and vomiting plus marked constipation. Finally, intussusception may occur, with acute obstruction and a palpable abdominal mass. This sequence is probable evidence of a pedunculated tumor of the small intestine.

Surgical operation is usually wholly successful.

A case of angiofibroma of the ileum with a double intussusception is presented. There are no previous reports of angiofibroma of the intestine.

2750 West North Avenue.
Norwegian-American Hospital.

14. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1942.

CHRONIC EFFECTS RESULTING FROM DOWNWARD TRACTION ON THE LIVER

WALTER M. BOOKER, PH.D.
PRAIRIE VIEW, TEXAS

I have described experiments in which circulatory failure was produced by maintaining a constant traction on the liver.[1] One is ordinarily prone, however, to think only of the acute effects of circulatory failure (hemoconcentration, loss of fluid, low blood pressure, rapid and thready pulse, etc.), without at the same time thinking of the chronic effects which may come after an animal has been subjected to periods of reduction of blood pressure, not to shock but to "preshock" levels. In this connection these questions present themselves: 1. What damage is done to the animal during relatively short periods of low blood pressure (50 to 60 minutes)? 2. If any damage occurs, is it reparable or irreparable? 3. What is the mechanism of the damage?

The purpose of this paper, therefore, is to present the results and interpretations of a number of experiments designed to produce chronic effects. Traction was exerted on the livers of dogs for short periods, and the animals were allowed to recover for observation.

METHODS OF PROCEDURE

A number of observations were made on the animals before and after operation. These observations included: general condition of the animal, water metabolism, urea content of the blood and urine, results of qualitative urinalysis, serum proteins, renal function (determined by urea clearance and dye tests), blood pressure and electrocardiographic characteristics. The observations made in the normal, or preoperative, period constituted control experiments for each animal used. This control, or normal, period of observation was usually ten days to two weeks.

At the beginning of the experiments to be reported here an attempt was made to apply traction for approximately the same period (about two hours) as was necessary to produce the beginning effects of circulatory failure in the experiments designed to produce acute effects. It was found, however, that many animals so treated failed to recover for sufficient time to allow desirable observations; hence a period was found for which traction could be kept on the liver and complete recovery obtained. This period ranged from fifty to sixty minutes.

The animals were operated on under anesthesia induced with soluble pentobarbital U. S. P. (pentobarbital sodium). Aseptic care was taken in all cases. After the incision was made the liver was pulled away from its approximation with the diaphragm and large pieces of sterile gauze were placed over it to prevent direct damage by the brass "hand" which was used to exert traction. The "hand" was then placed over the gauze-protected liver, and traction was exerted for fifty to sixty minutes continuously by tying the "hand" to the opposite end of the operating table. During this period the abdomen was covered with sterile towels, and at the end the "hand" was removed and the incision was closed.

CHEMISTRY OF BLOOD AND OF URINE

Urea.—Five cubic centimeter samples of blood were drawn two to three times a week in preoperative periods and daily after the operation for three weeks. Filtrates were prepared by sodium tungstate-sulfuric acid precipitation, and 5 cc. samples of the filtrate were used to

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From the Physiological Laboratory, the University of Chicago and the Biological Laboratories, Prairie View College.

A part of a dissertation submitted to the Division of Biological Sciences, Department of Physiology, the University of Chicago, in candidacy for the Ph.D. degree, September, 1942.

1. Booker, W. M.: Anesth. & Analg. **20**:237, 1941; **22**:93, 1943.

determine urea by the well known Van Slyke method. Urine was prepared by dilution (1 to 50 cc.) and filtration, after which 5 cc. samples of the filtrate were used to determine urea by the same method used for blood urea.

Serum Proteins.—Five cubic centimeter samples of blood were drawn at the same intervals as just described and allowed to clot, and after they had been centrifuged the serum was removed. One cubic centimeter samples of serum were used to determine the protein nitrogen by the Pragl steam distillation modification of the micro-Kjeldahl method.

Urinalysis.—Urine was tested for the presence of albumin by the Heller nitric acid ring test and was tested for bile pigments by the Gmelin nitric acid test.

TESTS OF RENAL FUNCTION

These tests were performed on female dogs, on which perineostomy had been performed in order to make the urethra easily accessible. The animals were trained to lie still during the tests, which required from one to two hours after the injection of 1 cc. of phenolsulfonphthalein. The same period was used for collection of blood and urine for urea clearance studies.

ARTERIAL BLOOD PRESSURE

Normal, or control, pressures were taken approximately twice a week for two to three weeks before operation. The animals were easily trained for manipulation of the needle into the artery

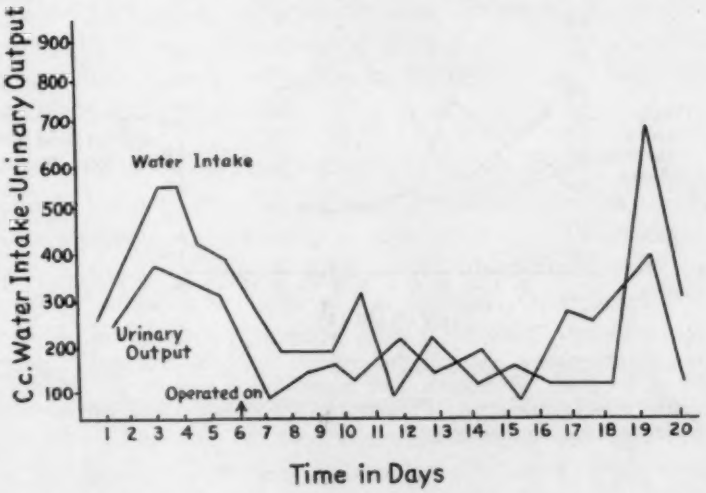

Fig. 1.—A typical experiment showing the water metabolism of an animal before and after traction on the liver.

(femoral), and after a few times little or no movement occurred when the needle was inserted. In the early postoperative weeks pressures were taken twice a week. Later they were taken once a week.

ELECTROCARDIOGRAPHIC STUDIES

Electrocardiographic records were taken several times before operation and at various postoperative intervals (once to twice a week). It was thought advisable, in view of the mobile character of the dog's heart, to change the positions of the animal on the table in preoperative tests (as control experiments) to see if rotation of the heart could possibly account for the changes in the contours of the records postoperatively. Records were taken (1) with the animal on its right side and the legs extended at right angles to the longitudinal axis of the body; (2) with the animal rotated slightly to the right and the feet extended upward; (3) with the animal flat on its back and the feet extended upward and in a few instances (4) with the animal on its left side.

INTERPRETATIONS AND RESULTS

During the first two or three postoperative days animals always showed depression and inactivity, a reduction or sometimes a complete loss of appetite and, of course, a loss of weight. Equally striking was the suppression of secretion of urine,

followed in time by pronounced diuresis (fig. 1). Later there were periods in which the output of urine again fell to 5 to 10 cc. a day and the urine was heavy with bile pigments. Such periods recurred about every three weeks.

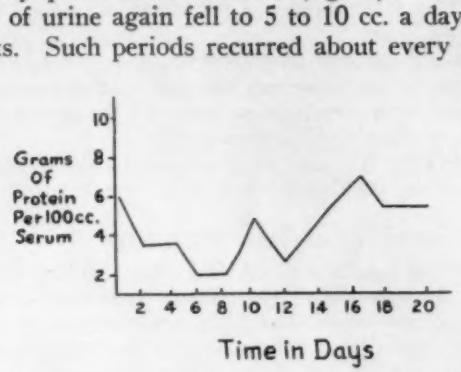

Fig. 2.—A typical experiment showing the changes in the serum proteins following traction on the liver. Preoperative or control values ranged between 6.0 and 6.5 Gm. per 100 cubic centimeters.

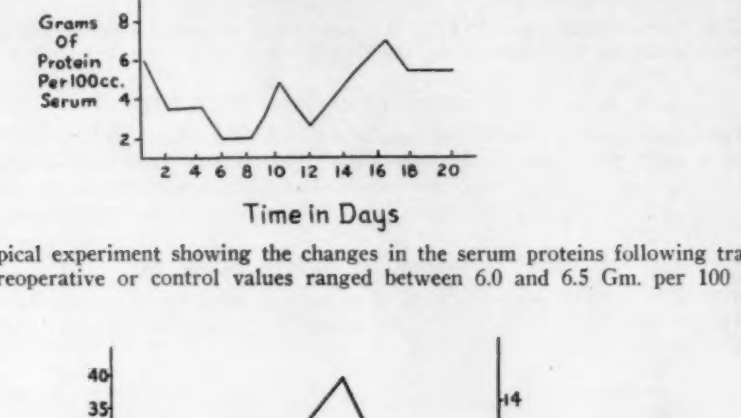

Fig. 3.—A typical experiment showing the changes in blood urea and blood amino acids following traction on the liver. Preoperative or control blood urea values ranged from 30.0 to 35.0 mg. per hundred cubic centimeters. Preoperative blood amino acid values ranged between 4 to 6 mg. per hundred cubic centimeters.

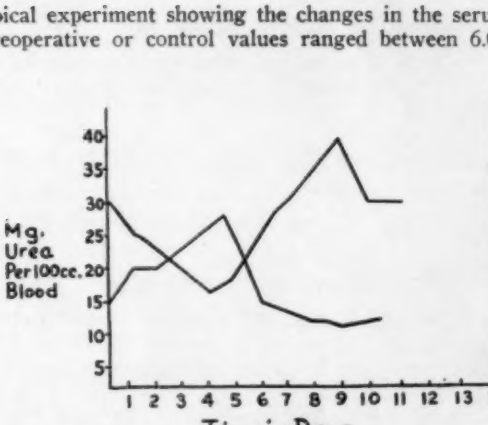

Fig. 4.—A typical experiment showing the changes in urinary urea following traction on the liver.

SERUM PROTEINS

The sharpest changes in the serum proteins occurred the first postoperative week, as can be seen in figure 2. The urine in this and subsequent weeks was positive for albumin, and this would seem to indicate that damage was done to the

kidneys during the period of traction on the liver. It seems safe to say that the fall in the serum proteins can be accounted for by the route of the kidney. The loss of albumin was not spasmodic; rather there was a daily loss. It therefore seems amazing that there was a return of the serum proteins to preoperative or even higher levels after two weeks. It is probable that the recovery of the liver from temporary functional damage (to be discussed hereinafter) made possible a high output of plasma proteins after a week, sufficient to cope with the loss of albumin from the kidney and perhaps in the peritoneal cavity.

BLOOD AND URINARY UREA AND AMINO ACIDS

It was suspected that in view of definite suppression of secretion of urine there might be damage to the kidneys adequate to cause retention of urea. Surprisingly, however, the blood urea did not increase but decreased, as did also the urinary urea (figs. 3 and 4). In view of the work of Bollman and Mann [2] and later of Mann,[3] clearly pointing out the liver as the source of urea formation, it was thought that perhaps the liver was functionally damaged during traction and that there might be, as a result, reduction in urea formation. To prove this, attention was turned to the blood amino acids. Figure 3 shows that the increase in amino acids is concomitant with the decrease in blood urea; when the concentration of urea rises that of amino acids falls.

DYE AND UREA CLEARANCE TESTS

These tests failed to show significant differences between the function of the kidney postoperatively and its function preoperatively. In all cases dye appeared in the urine in about six minutes after it was injected and after an hour normal percentages of dye had been excreted. It must be remembered that there is considerable reduction in urea formation during the first postoperative week, and in this period particularly the urea clearance test is not reliable. In a general way the results of the clearance tests in these experiments are in agreement with the work of Corcoran and Page [4] and of other investigators who were unable to note distinct changes in the results of clearance tests unless the blood supply to the kidney was almost shut off by the arterial clamp.

It is interesting, in the matter of damage to the kidney, that Penner and Bernheim [5] in 1940 described bilateral cortical changes in the kidney in patients who had come to autopsy and whose histories showed they had experienced periods of low blood pressure or even shock. Penner and Bernheim were able to reproduce these changes in dogs experimentally by subjecting them to periods of low blood pressure. They expressed the opinion that the alterations were due to reflex vasoconstriction sufficient to produce ischemic necrosis of the kidney. During the studies now being reported, histologic examination of sections from the kidney revealed mild but definite damage, reflected in fatty degeneration of the tubular cells and thickening of Bowman's capsule (fig. 5).

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2. Bollman, J. L., and Mann, F. C.: Am. J. Physiol. **92**:92, 1930.

3. Mann, F. C.: The Liver and Medical Progress, J. A. M. A. **117**:1577 (Nov. 8) 1941.

4. Corcoran, A. C., and Page, I. H.: (*a*) Am. J. Physiol. **126**:354, 1939; (*b*) J. Lab. & Clin. Med. **26**:1713, 1941.

5. Penner, A., and Bernheim, A. I.: Acute Ischemic Necrosis of the Kidney, Arch. Path. **30**:465 (Aug.) 1940.

Fig. 5.—Photomicrograph of a histologic section of a kidney removed from an experimental animal brought to autopsy. Traction had been exerted on the liver several months before the section was made. Note the degeneration of the tubular epithelium. Free-hand sections removed from this kidney stained positive for fat in sudan III. × 400.

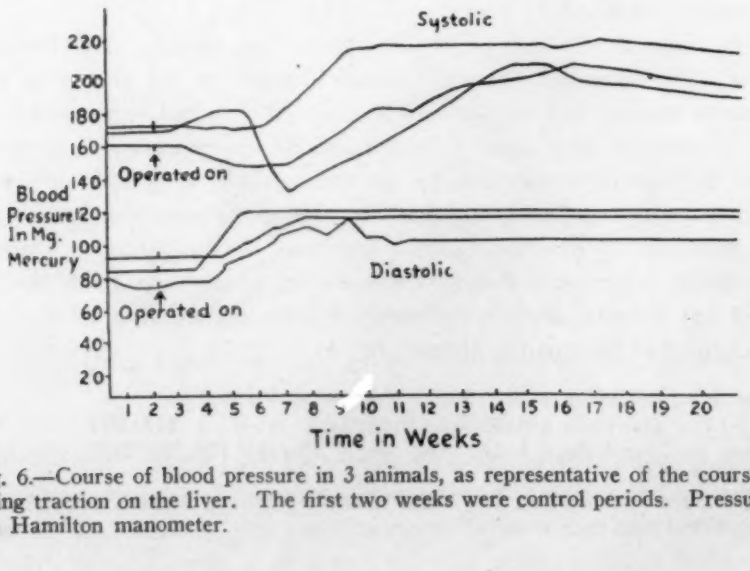

Fig. 6.—Course of blood pressure in 3 animals, as representative of the course in 7 animals, following traction on the liver. The first two weeks were control periods. Pressures were taken on the Hamilton manometer.

HYPERTENSION

Stimulated by the classic work of Goldblatt and his co-workers [6] and by that of Page and Corcoran and many others, I decided to follow the course of blood pressure in a number of animals to determine if renal hypertension could be demonstrated as a result of damage to the kidney during traction on the liver. It will be noticed in figure 6 that significant rises in both systolic and diastolic blood pressure can be seen.

Recently Corcoran and Page [4b] made important contributions to the subject of hypertension of renal origin. They expressed the opinion that in the "Goldblatt kidney" there is a reduction of pulse pressure and not of blood flow, unless the clamp is made very tight, and that reduction of pulse pressure is the chief cause of damage to the kidney in such cases. They pointed out that "organs perfused in the absence of pulsatile flow become edematous and their cells may lose their normal permeabilities to vital dyes." The mechanism of the damage is by no means clear, but it is sufficient to cause the release of a pressor substance which subsequently accounts for the maintained hypertension. It seems important from the point of view of the present work that from reduction either of blood flow or of pulse pres-

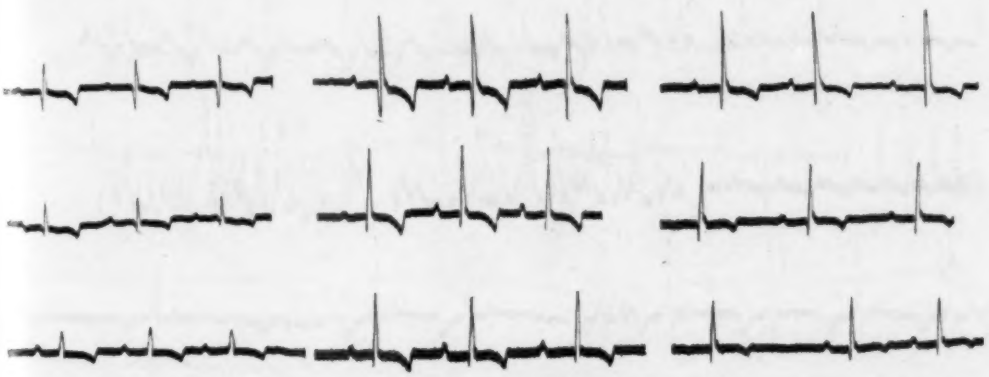

Fig. 7.—A typical experiment showing the effect of changes in position of the animal on the contours of the electrocardiograms. This control experiment was designed to obviate the possibility that changes in position of the heart might account for the changes in the contours of the electrocardiograms after traction on the liver.

sure there is established in the kidney during the brief period of low arterial and high venous pressure an anoxic condition adequate to cause renal damage and release of a pressor substance.

At least two ideas of pressor mechanisms have been advanced: 1. Corcoran and Page [4b] postulated that renin, formed as a result of damage to the kidney, is acted on by a renin activator, producing angiotonin—itself the pressor substance. Interestingly, a counteraction may take place, in which a renin inhibitor is relased by undamaged cells and prevents the liberation and pressor action of angiotonin. Furthermore, repeated injections of renin or angiotonin result in failure of the blood pressure to rise because of the formation of the renin inhibitor—producing what is called tachyphylaxis. 2. Houssay [7] and Braun-Menendez, Fasciola, Leloir and Muñoz,[8] on the other hand, described a different sort of humoral mechanism. They

6. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: Am. J. Path. **9**:942, 1933.

7. Houssay, B. A.: Medicina, Buenos Aires **1**:167, 1941.

8. Braun-Menendez, E.; Fasciola, J. C.; Leloir, L., and Muñoz, J. M.: Rev. Soc. argent. de biol. **15**:420, 1939.

expressed the opinion that renin (itself not vasoactive) is liberated from damaged kidneys and acts on a pseudoglobulin, "hypertensinogen" to produce "hypertensine," which is vasoactive. They described an inhibitory substance, "hypertensinase," which prevents the action of "hypertensine." In essence these two theories of humoral mechanism agree, although a different terminology is employed.

It is, however, beyond the scope of this paper to enter into full discussion of the case for the humoral mechanisms in the cause of hypertension. It seems clear that some substance is liberated from a damaged kidney, or perhaps from certain cells of a damaged kidney, which causes a maintained vasoconstriction. In these

Fig. 8.—A typical experiment comparing the cardiac effects of traction on the liver on unatropinized animals with similar effects on those treated with atropine.

experiments, the important question is: Why must two or three weeks elapse before there are significant rises in blood pressure? There seem to be two possibilities: 1. The undamaged cells of a kidney are liberating an inhibitor substance which is able to prevent for a while the rise in blood pressure. This might find support in the results of the experiments of Goldblatt and his associates, in that the tighter the clamp the greater the damage and the faster and higher the rise in blood pressure. 2. Recently Page, McSwain; Knapp, and Andrus [8a] have shown that the renin

8a. Page, I. H.; McSwain, B.; Knapp, G. M., and Andrus, W. deW.: Am. J. Physiol. **135**:214, 1941.

activator probably comes from the liver and in animals with a damaged liver or in hepatectomized animals there is failure of the blood pressure to rise following clamping of the renal artery. In this paper it has been established that there is perhaps a temporary functional damage of the liver lasting at least a week, and it does not seem far fetched, therefore, to postulate the view that the slow rise in blood pressure may be due to failure of the liver to liberate the renin activator during damage.

THE HEART

In early experiments it was observed in an animal at autopsy that there was an unusual hardness at the tip of the left ventricle, which on histologic examination revealed what was described as nuclear degeneration and necrosis. Later by crude auscultation it was revealed that animals always had slow and extremely arrhythmic

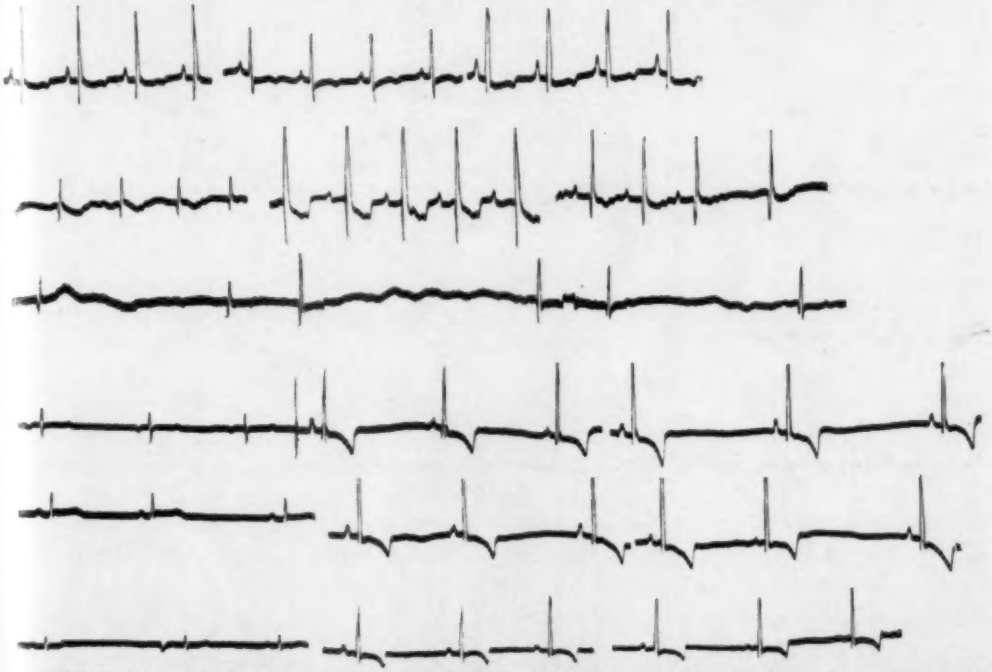

Fig. 9.—A typical experiment comparing the prolonged cardiac effects of unatropinized animals with those atropinized. Animals were treated with atropine before traction was exerted on the liver.

heart action after operation. It was then decided to make electrocardiograms on a number of animals to determine what changes could be observed in postoperative periods from the conditions noted in the same animals before operation. It may be seen in figure 7 that changes in the position of the animal do not cause significant changes in the contours of the electrocardiograms.

While this work was in progress, the work of Blumgart, Gilligan and Schlesinger [9] appeared in which these investigators described ventricular fibrillation and extrasystoles resulting from temporary occlusion of a single coronary artery for varying periods. And they went further, to describe structural changes in the myocardium following (by a few days) the occlusions.

9. Blumgart, H. L.; Gilligan, D. R., and Schlesinger, M. J.: Am. Heart J. **22**:374. 1941.

The problem, however, became one of explaining just how such changes in the normal function of the heart as are probable from the contours of the electrocardiograms shown in figure 8 could occur, since this work did not involve the heart or its blood vessels directly, as did that of Blumgart, Gilligan and Schlesinger. The theory seemed attractive that the changes were due to decreased venous return to the heart, which reduced the cardiac output and the coronary inflow. As a matter of fact, Wiggers [10] in his recent review on the problem of shock pointed out that in shock there is depression of the myocardium which results from decreased cardiac output, although Katz (personal communication) objected to the view that coronary flow can be predicted from the cardiac output. Another, and more attrac-

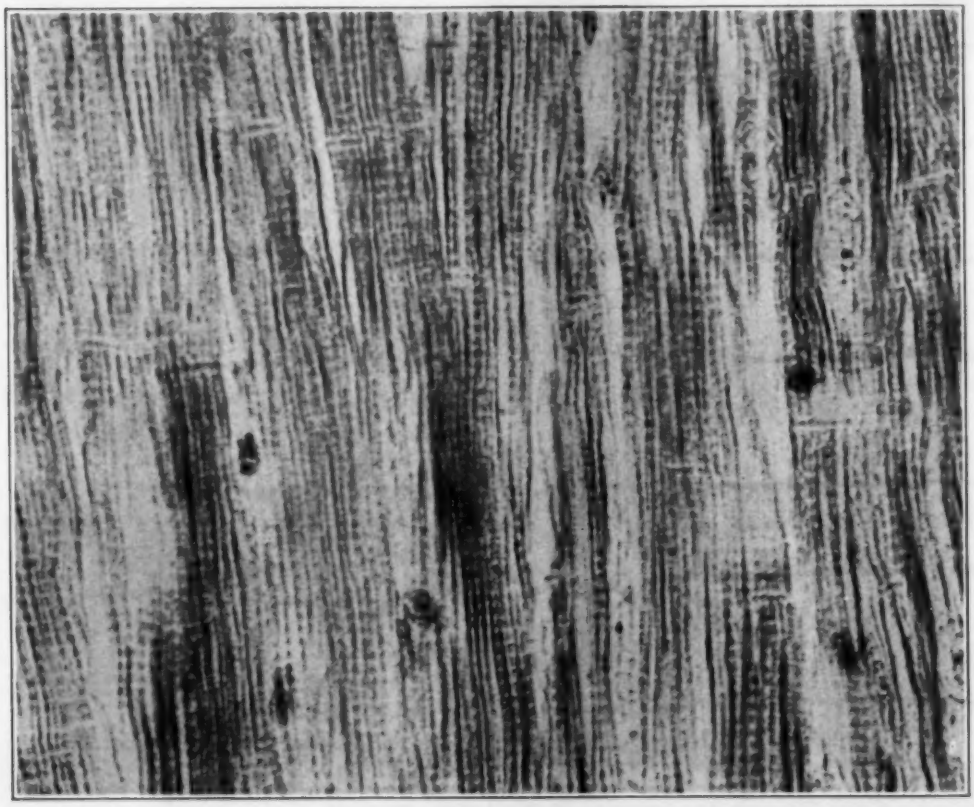

Fig. 10.—Photomicrograph of a histologic section of heart taken from an animal in which traction had been exerted on the liver. Note the nuclear degeneration. × 400.

tive, point of view, however, was that the coronary arteries are supplied with vasoconstrictor fibers carried by the vagi (Lingle-Porter); and it seemed worth while to test the possibility that constriction of the coronary arteries might occur and act to reduce the blood supply to the heart. Thus blocking the action of the vagi with atropine should prevent constriction of the coronary arteries as well as the changes that occur in the electrocardiograms of the untreated animals (figs. 8 and 9). That the theory of vagal involvement during traction is tenable finds support in the work of Gilbert,[11] who described interesting experimental and clinical observations on

10. Wiggers, C. J.: Physiol. Rev. **22**:74, 1942.
11. Gilbert, N. C.: Bull. New York Acad. Med. **18**:83, 1942.

cardiac changes in dogs and in patients who had experienced different types of abdominal distention. He reported that patients who had hiatus hernias, and whose stomachs were definitely displaced and distended were known to experience anginal attacks and that patients with angina themselves were extremely susceptible to attacks immediately after a heavy meal. Atropinized animals failed to show extrasystoles or fibrillations when the stomach was distended with air, while the untreated animals showed such abnormalities.

The point advanced by Gilbert is that a vagal reflex is set up when the abdominal viscera are severely distended which acts to cause constriction of the coronary arteries and a corresponding reduction in the blood supply to the myocardium (causing a partial anemic infarct). This indeed seems to be a fitting explanation for the results described in this paper, although the histologic examination of the hearts taken from some of the animals failed to reveal more than nuclear degeneration (fig. 10).

SUMMARY AND CONCLUSIONS

Experiments are described which show the chronic effects resulting from downward traction on the liver.

The evidence seems to show that damage is done to the kidneys. The injury is probably produced by passive congestion (although possible reflex vasoconstriction is not to be excluded), and the result is renal hypertension which persists for months.

The changes in the contours of the electrocardiograms seem to point to the view that traction on the liver results in a derangement of the normal function of the heart, both during traction and weeks after. And there is mounting evidence that such manipulation sets up a reflex over the vagus nerve, which causes constriction of the coronary vessels, reducing blood supply and probably causing damage to the myocardium.

Apparently atropine blocks the reflex, for in atropinized animals no significant changes in the electrocardiograms occur either during traction or subsequently. (Such observations seem to indicate that atropine should be used in abdominal surgery not only for drying secretions but for eliminating the cardiac reflex).

Comparative histologic examination of sections from the myocardium of dogs which had been subjected to traction on the liver and similar sections from controls reveal apparent nuclear degeneration in the former.

Dr. Arno B. Luckhardt gave helpful suggestions for the carrying out of this study. Dr. G. W. Bartelmez prepared and interpreted the histologic material. Mr. Richard Johnson gave valuable technical assistance. Dr. Julian Lewis was responsible for some of the observations on the myocardium.

Prairie View College.

REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES
FRANK HINMAN, M.D.
SAN FRANCISCO
ALEXANDER VON LICHTENBERG, M.D.
MEXICO, MEXICO
ALEXANDER B. HEPLER, M.D.
SEATTLE
ROBERT GUTIERREZ, M.D.
NEW YORK
GERSHOM J. THOMPSON, M.D.
AND
EDWARD N. COOK, M.D.
ROCHESTER, MINN.
EGON WILDBOLZ, M.D.
BERNE, SWITZERLAND
AND
VINCENT J. O'CONOR, M.D.
CHICAGO

KIDNEY

Tumor.—Foulds [1] reports a case of renal tumor containing elements of malignant papillary cystadenoma and papillary carcinoma with clear cells. This case with other recorded cases illustrates the transition from renal adenoma to malignant cystadenoma and eventually, in some instances, to papillary carcinoma with clear cells.

The patient, a man 59 years of age, complained of pain and hematuria. The kidney was removed, and the patient recovered without difficulty. The kidney measured 13 by 7 by 4.5 cm. and weighed 225 Gm. The outer surface was slightly roughened and reddened. The capsule was thin and stripped with difficulty; the stripping left a finely granular surface. In the upper pole of the kidney, projecting into a calix, there was a soft red mass, measuring 4.5 cm. in length and 2.5 cm. in its greatest width. Microscopically the tumor was composed of papillary processes covered with small cuboidal cells, with deeply stained round or polyhedral nuclei. These processes projected into and nearly filled irregular cystic spaces. The stroma was densely fibrous. In one preparation made from the material removed for quick section, from the center of the tumor, small areas were found in which the cells were large and their cytoplasm clear or foamy. Small blood vessels were fairly numerous, and several small areas of calcification were seen. These areas in both the character and the arrangement of the cells presented a picture typical of papillary carcinoma with clear cells, the so-called hypernephroma. Preparations made from the edge of the tumor showed slight invasion of the adjacent renal tissue. There was hyperplasia of fibrous tissue between the tubules. Although the epithelium of the pelvis was reflected onto the edge of the tumor, it did not cover the projecting tumor. Sections taken from the remainder of the kidney showed little

1. Foulds, G. S.: An Unusual Kidney Tumor: Malignant Papillary Cystadenoma and Papillary Carcinoma with Clear Cells, J. Urol. **48**:131-135, (Aug.) 1942.

of note except that the intima of the arterioles was thickened. The pathologic diagnosis was malignant papillary cystadenoma and papillary carcinoma with clear cells.

Beilin and Neiman [2] state that bilateral renal carcinoma in the adult is rare. They report the case of a man aged 50 years. The diagnosis of hypernephroma on the left side was made and the kidney removed in July 1933. Microscopic examination revealed hypernephroma. Six years later a diagnosis of renal tumor on the right side was made. Necropsy showed that the growth in the right kidney also was a hyperephroma.

Vitt and Melick [3] review 6 cases of hypernephroma of the kidney as a complication of pregnancy which have been reported in the literature and add a case of their own. The diagnosis of renal tumor should be made, if possible, before the classic triad of pain, mass in the loin and hematuria have appeared. However, even if these are present operation in carefully selected cases can prolong life. Whether the growth of renal tumors is accelerated by coexisting pregnancy and the lesion is more likely to metastasize during pregnancy cannot be settled definitely. Pregnancy usually is not terminated by removal of a kidney and is not a contraindication to operation, provided the other kidney is normal. Further pregnancies are possible, provided that the function of the remaining kidney is normal and every precaution is taken during the subsequent pregnancies to watch for, and to guard against, renal insufficiency and infection.

Colvin [4] studied and tabulated the characteristics of 164 capsulomas (small, benign, mixed capsular and subcapsular tumors of the kidney) in 144 of 2,634 consecutive patients who came to necropsy at the Mayo Clinic—an average incidence of 5.5 per cent in the period of four years covered by the study. The incidence apparently varies in proportion to current interest. Ninety-nine per cent of the 164 patients were more than 40 years of age. There was no appreciable variation in sex incidence. From one to three capsulomas were found per patient, but the majority were single. Capsulomas occurred with approximately equal frequency in the right and the left kidney. They were located in or just under the renal capsule. Their diameters varied from 1 to 5 mm. Histologically, they contained two basic elements, smooth muscle and fibrous tissue, although a certain proportion contained fat and epithelial elements. All tumors in this series were benign; they were apparently of no clinical significance and were discovered incidentally at necropsy. According to the evidence gathered, it is believed that capsulomas are true tumors; some are derived from the capsule, some from nephrogenic rests and a few from the walls of blood vessels.

Stone.—Dourmashkin and Solomon [5] state that lithiasis of the upper part of the urinary tract is a common complication of urethral stricture. It occurred in 22.6 per cent of cases in their series. In 6 of the 9 cases of renal stone and in 2 cases in which advanced renal lesions other than stone were present, renal pain was absent; the lesions were discovered through routine roentgen examination. Because patients who have stricture are of the transient type, Dourmashkin and Solomon

2. Beilin, L. M., and Neiman, B. H.: Bilateral Renal Carcinoma, J. Urol. **48**:575-584 (Dec.) 1942.

3. Vitt, A. E., and Melick, W. F.: Carcinoma of the Kidney and Pregnancy, J. Urol. **48**:601-610 (Dec.) 1942.

4. Colvin, S. H.: Certain Capsular and Subcapsular Mixed Tumors of the Kidney Herein Called "Capsuloma," J. Urol. **48**:585-600 (Dec.) 1942.

5. Dourmashkin, R. L., and Solomon, A. A.: Upper Urinary Tract Lithiasis: A Frequent Complication of Urethral Stricture, J. Urol. **48**:196-203 (Aug.) 1942.

suggest that an immediate roentgen examination of the urinary tract should be done when the diagnosis of a stricture is established.

Hypertension and Renal Lesions.—Ratliff and Conger [6] present statistics based on a series of 528 consecutive hypertensive persons. Unsuspected lesions of the kidney were demonstrated in a low but sufficiently high percentage of cases to warrant continuance of routine pyelographic studies in cases of asymptomatic hypertension as well as in cases in which urinary symptoms are present.

Ratliff and Conger evaluate the results of nephrectomy in selected cases of hypertension. They consider that the point of major importance is the selection of the case. For the time being, and until a more selective test has been adopted, a policy should be adopted that nephrectomy should be performed in any case of hypertension in which unilateral renal disease can be demonstrated, not only in order to cure the local lesion but in the hope that the hypertension will be relieved.

Braasch and Wood [7] report a survey of the records of 70 cases of clinical perinephritis in an effort to determine the effect of this condition on blood pressure. Fifty-two of the 70 patients were males, and 18 were females—a ratio of 2.89 to 1. The mean age for the group was 38.3 years. Eighty-one and four-tenths per cent of the group were less than 50 years of age. In 67 of the cases the diagnosis was verified through surgical exploration; in the 3 remaining cases the clinical and urographic evidence was sufficient to warrant the diagnosis, although the treatment was conservative.

Six patients were classed as hypertensive by virtue of elevation of the systolic or diastolic blood pressure or both. This is an incidence of 8.6 per cent. In 2 of these 6 cases, however, conclusive evidence was present that hypertension had existed prior to onset of the perirenal disease. One of these patients had known for twenty years that he had hypertension; the other, for at least two years. In a third case other factors apparently were operating to influence the arterial blood pressure and, although the blood pressure was 114 mm. of mercury systolic and 90 mm. diastolic at the time of drainage of the perirenal abscess, one year later it had increased to 148 mm. systolic and 90 diastolic. Thus only 3 cases remain in which association of perinephritis and elevated arterial blood pressure might be present, an incidence of but 4.3 per cent.

A second group of cases of perinephritis secondary to some primary renal disease, such as renal lithiasis or hydronephrosis or both, or pyonephrosis, was reviewed for evidence of association of elevated blood pressure. The cases in this group were selected according to the degree of perinephritis present, the blood pressure being ignored until the group analysis was begun. In 28 cases the perinephritic reaction was considered to be of sufficient degree to warrant inclusion in this group. In 6 (21.4 per cent) of these 28 cases, hypertension was present.

Aneurysm.—Child [8] presents a case of aneurysm of the renal artery, which brings the total number of reported cases to 75. The chief interest in this lesion, aside from its rarity, lies in the confusion of the wreathlike shadow of calcium density seen in this case with that cast by a gallstone, which led to an erroneous preoperative diagnosis and an unnecessary celiotomy. A careful study of this patient's preoperative and postoperative blood pressure failed to reveal any relationship between them and the aneurysm.

6. Ratliff, R. K., and Conger, K. B.: The Incidence of Renal Hypertension and of Cure by Nephrectomy, J. Urol. **48**:136-141 (Aug.) 1942.

7. Braasch, W. F., and Wood, W. W., Jr.: Clinical Perinephritis and Its Effect on Blood Pressure, J. Urol. **48**:343-349 (Oct.) 1942.

8. Child, C. G., III: Aneurysm of the Renal Artery: A Case Report, J. Urol. **48**:142-146 (Aug.) 1942.

Ischemia.—Hoffman [9] reports a case of renal ischemia produced by aneurysm of the abdominal aorta. The patient was a Negro aged 28 years who had late syphilis. He was dyspneic and died from congestive heart failure. At necropsy an aneurysm about 6 cm. in diameter was found extending out from the left side of the abdominal aorta. This aneurysm pressed on and stretched the vessels of the left kidney and considerably diminished the lumen of the renal artery. About half of the aneurysm was filled with blood clot. The left kidney weighed only 80 Gm.

This case is interesting in that the conditions which Goldblatt produced in his experimental work on dogs also were produced in this case. The blood pressure was 190 mm. systolic and 117 diastolic, quite possibly owing to the ischemia of the left kidney and renal damage caused by the diminution in size of the lumen of the left renal artery.

Life After Nephrectomy.—From a review of the data obtained in his study of cases of nephrectomy, Kretschmer [10] makes the following statements:

The average length of time that elapsed between nephrectomy and examination was eight years and two months. The longest period since the nephrectomy in his series was twenty-four years and eleven months.

The oldest patient at the time of nephrectomy was 72 years of age; one year and eight months had elapsed since the operation. The oldest patient studied in this series was 77 years of age; a period of sixteen years had elapsed since the operation. The youngest patient at the time of nephrectomy was 10 months of age; a period of four years and six months had elapsed since the operation.

Pain in the remaining kidney does not occur with any great regularity, although the impression seems to prevail that this phenomenon is common after nephrectomy. It occurred in only 7 cases in this series. In some of the cases in which it occurred, a pathologic condition in the remaining kidney, disclosed by study, was responsible for its presence.

Eighteen patients (11.5 per cent) had cardiac involvement, 4 of whom were less than 50 years of age. One patient had cardiac hypertrophy before operation. The incidence of cardiac enlargement in a group of patients more than 50 years of age after nephrectomy is therefore about what one can expect in a group of persons of similar ages who had not undergone nephrectomy.

In the largest number of cases weight remained the same or there was an increase. In only 5 was there a loss. A gain of as much as 50 pounds was noted in 7 cases.

In 14 cases there was an increase in the blood pressure. After elimination of the cases in which hypertension was present before operation, the study discloses that the patients were well along in years, having reached a time in life when hypertension might be expected.

The results of urinalysis depend on the lesion for which the nephrectomy was performed. Of the 49 cases of renal tuberculosis, pus was present in 14 and albumin in 6. Of the 42 cases of stone, pus was present in 11 and albumin in 6, whereas in the remaining groups of 65 cases pus was present in 11 and albumin in 6. The cultures were more frequently positive in the group of cases in which nephrectomy had been performed for stone. All cultures of urine in the cases of tumor were sterile. Cultures of urine were positive in 4 cases in the miscellaneous group, in 11 cases of hydronephrosis and in 14 cases of tuberculosis.

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9. Hoffman, B. J.: Renal Ischemia Produced by Aneurysm of Abdominal Aorta, J. A. M. A. **120**:1028-1030 (Nov. 28) 1942.

10. Kretschmer, H. L.: Life After Nephrectomy, J. A. M. A. **121**:473-478 (Feb. 13) 1943.

Studies of the nonprotein nitrogen content of the blood were made in 146 of the 156 cases. The value was increased in 36 (24.65 per cent).

Seventy-three per cent of the patients with only one kidney were able to pass the Newburgh concentration test.

Circulation and Pitressin.—Wakim, Herrick, Baldes and Mann [11] studied the effect of pitressin on renal circulation and urinary secretion of frogs and dogs. Various dilutions of pitressin were administered to anesthetized frogs by three methods—direct application to the kidney, injection into the dorsal lymph sac and injection into the abdominal vein. By means of transillumination, direct observations were made on the glomerular tuft of capillaries and other vessels. These authors found that pitressin produced cessation of circulation in the glomerular tuft and slowed the circulation in the other vessels for a fraction of a minute to several minutes, depending on the amount and dilution of pitressin used.

Two groups of dogs under different types of anesthesia were given pitressin by various methods. Simultaneous records of urine formation and renal blood flow and optical records of blood pressure were made. No changes were noted when pitressin was administered subcutaneously. Intramuscular administration produced only slight changes. When pitressin was injected intravenously, transient anuria resulted and was followed by oliguria and marked decrease in renal blood flow and a sudden transient rise in blood pressure which was eventually followed by a gradual but moderate rise. The authors conclude that the intravenous administration of pitressin invariably decreases the blood flow and urge caution when using the drug in this manner to prevent untoward effects.

URETER

Tumor.—Moore [12] states that both benign and malignant neoplasms occur in the ureter, but the latter are much more common and may be of either epithelial or connective tissue origin. For simple papilloma, if adequate care is taken not to infect other tissues at operation, the prognosis is good. The outlook for carcinoma is bad. The growth is usually advanced before the diagnosis is made, and there is a considerable immediate operative mortality. The only rational treatment is complete ureteronephrectomy. This usually can be performed safely in one stage with the patient under spinal anesthesia. When the complete operation is performed, there are two ways of dealing with the lower end of the ureter. It may be excised with a small portion of vesical wall, or the extreme lower end may be left, its mucosa being destroyed by diathermy before ligature in order to destroy any neoplastic deposits in it.

Moore reports the case of a man aged 25 years who had pain in the left renal area for fifteen months. Intravenous urography revealed some dilatation of the lower part of the left ureter, which had a peculiar mottled appearance. Complete nephroureterectomy was done except for the lowest ¼ inch (0.64 cm.) of the ureter. The mucosa of the lower end of the ureter was destroyed with diathermy before ligation. Microscopic examination showed a simple papilloma of the ureter.

Moore also reports a case in which retrograde ureterograms showed an irregular obstruction in the middle of the left ureter of a man aged 57 years. At operation a hard nodule was found in the middle portion of the left ureter. The ureter was

11. Wakim, K. G.; Herrick, J. F.; Baldes, E. J., and Mann, F. C.: The Effect of Pitressin on Renal Circulation and Urine Secretion, J. Lab. & Clin. Med. **27**:1013-1022 (May) 1942.
12. Moore, T.: Tumors of the Ureter, Brit. J. Surg. **29**:371-377 (April) 1942.

ligated below this and mobilized as high up as possible. The wound was closed and the operation completed through the ordinary oblique kidney incision. The growth in this case was malignant.

Sauer [13] reports a case of metastasis to bone from carcinoma of the ureter complicated by congenital hydronephrosis. The patient was a man 56 years of age who gave a history of pain in the right loin and a tumor mass in the right side of the abdomen. After cystoscopic examination, a diagnosis was made of tumor of the right kidney with metastasis to the right humerus. The patient died and two different conditions were found: one was a combination of congenital anomalies; the other was carcinoma of the ureter which had metastasized to the right humerus and to the left kidney. There was complete duplication of the renal pelvis and ureter on the left side, with the calices of the lower renal pelvis pointing toward the midline. On the right side massive hydronephrosis was found, which obviously was due to congenital stricture at the ureteropelvic junction. The hydronephrotic sac contained 1,500 cc. of bloody, foul-smelling urine. The lumen of the middle third of the right ureter was filled by a papillary tumor which was 4.5 cm. long and from 2.3 to 2.8 cm. wide. A distance of 1.5 cm. separated the upper border of the tumor from the stricture at the ureteropelvic junction. No infiltration of the ureteral wall by the tumor was apparent between the stricture and the upper border of the neoplasm. Examination of the right humerus revealed almost complete replacement of its uper third by tumor tissue. The lesion, which was 12.5 cm. long and 8.5 cm. wide, had the macroscopic appearance of an osteogenic sarcoma. No other metastatic lesions were found except a small one in the left kidney. Microscopic examination of the primary tumor revealed papillary carcinoma of the squamous cell type, which had invaded the deeper layers of the ureteral wall. Sections from the lesions of the right humerus and the left kidney showed the same histologic structure as the primary growth.

Riches [14] reports a case of carcinoma of the ureter in a woman 46 years of age. Excretive urography revealed a small calculus in the lower end of the right ureter with some dilatation of the kidney and extensive hydronephrosis of the left renal pelvis. The stone was passed after cystoscopic manipulation, and further catheterization revealed an obstruction 15 cm. above the orifice. A diagnosis of ureteral tumor was made and nephro-ureterectomy carried out. In the ureter there was a firm fusiform mass to which the overlying peritoneum was adherent. The specimen removed showed a hydronephrotic kidney, with dilatation of the upper portion of the ureter and a papillary growth which constricted the ureter directly below this. Recurrence developed, and the patient died several months later.

Transplantation.—Jewett [15] discusses a new method of ureteral transplantation. At the first operation, the intestinal bed is prepared for the ureter. The incision, 5 cm. in length, is carried down to the submucosa. The lateral edge of the incision is peeled up for a distance of 0.5 cm., and the medial edge, for 2 mm. The ureter is completely extraperitonealized. Both ureters are buried in the wall of the bowel and left connected with the bladder at the first operation. No communication is made between the ureter and the intestinal lumen at this time. Three weeks later the second operation is carried out. The ureter is cut off from its

13. Sauer, H. R.: Case of Large Bone Metastasis from Carcinoma of the Ureter Complicated by Congenital Giant Hydronephrosis, J. Urol. **48**:467-473 (Nov.) 1942.

14. Riches, E. W.: A Case of Primary Carcinoma of the Ureter, Brit. J. Surg. **29**:392-393 (April) 1942.

15. Jewett, H. J.: A New Method of Ureteral Transplantation for Cancer of the Bladder: A Report of Fifteen Clinical Cases, J. Urol. **48**:489-509 (Nov.) 1942.

connection with the bladder; the lower end is ligated, and an electrode is placed in the lower end of the ureter to burn through into the intestinal lumen.

Jewett carried out this procedure with a specially insulated electrode in a series of 15 cases. Nine of the patients are now living, and the longest postoperative interval is eighteen months. Of the 6 patients who died, 3 died during convalescence and 3 later. Four had complications which required further operations. Laparotomy in 1 case disclosed volvulus of the intestine. In the second case the ureteral stump was torn out of its intestinal tunnel at the second stage, and eventually cutaneous ureterostomy had to be done. Excessive traction was the cause, and this has been avoided in succeeding cases. In the third case a chronic pelvic abscess occurred and was drained three and a half months after cystectomy. The subsequent course was entirely uneventful. The fourth case was that of a middle-aged woman who had had eight previous abdominal operations. On the left side there were chronic pyelitis and ureteritis prior to transplantation, and the urine contained Streptococcus faecalis. After the second stage of the transplantation of the left ureter, some intra-abdominal extravasation of urine occurred, which required drainage and subsequent nephrectomy. Further progress of the patient has been satisfactory.

BLADDER

Tumor.—Spencer [16] reports a case of mucoid adenocarcinoma of the urinary bladder and gives a résumé of the literature. The patient was a young man aged 23 years. Cystoscopy revealed an encrusted tumor of the right anterior wall of the bladder. At operation a growth the size of a walnut was found in the apex of the bladder. The tumor was excised and the wall of the bladder sutured. Histologic examination revealed mucoid adenocarcinoma. Two and a half years later the tumor recurred and a hard, fixed suprapubic mass was found. A second operation was carried out.

Graham [17] discusses ectopia vesicae complicated by adenocarcinoma and reviews the literature. Ectopia vesicae is an uncommon congenital deformity. Fifty per cent of all persons afflicted with exstrophy are dead by their tenth year, and 66.67 per cent are dead by their twentieth year. In one series reported in the literature, out of 74 patients not operated on, only 23 passed the twentieth year of life. It is estimated that about 10 per cent reach maturity, and in a few of this number carcinoma of the exposed bladder develops.

Tumors of the adenomatous type are rare in the normal bladder. Tumors most closely resembling those found in the ectopic bladder are found at the apex of the bladder. The structure of the wall of the ectopic bladder presents a different appearance from that of the normal bladder. Superficially there are thickening and keratinization of the epithelium which cause it to resemble epidermis, while in the deeper layers is glandular tissue formed by high cylindric epithelium, with mucus-containing goblet cells. This glandular formation, which has been noted in all the cases in which microscopic examination has been performed, would appear to be usual to the ectopic bladder, whereas it is exceptional in the normal bladder. Thus the high incidence of adenocarcinoma of the intestinal type in the ectopic bladder is accounted for.

In order to verify the statements and to offer some explanation as to the origin of the adenomatous tissue, a small series of ectopic bladders from patients of varying ages was collected and histologic examination was carried out by Graham.

16. Spencer, H.: Mucoid Adenocarcinoma of the Urinary Bladder, Brit. J. Surg. **29**: 400-402 (April) 1942.

17. Graham, W. H.: Ectopia Vesicae Complicated by Adenocarcinoma, with a Review of the Literature, Brit. J. Surg. **30**:23-32 (July) 1942.

The bladder of the youngest patient, aged 4 months, revealed a transitional cell lining which was hyperplastic and keratinized in places. Transitional cell epithelial nests were seen deep in the hyperplastic lining, and one had undergone cystic change. In the same sections a larger cyst could be seen, the lining, of which, although of transitional cells, was somewhat modified. The specimen of bladder from a child 6 years old had a lining which in places was keratinized and squamous in character. There were numerous cystic spaces, some lined by transitional epithelium and others by a single layer of flattened epithelial cells. One area contained glandular tissue lined by tall columnar celled mucin-secreting epithelium. Two specimens from patients aged 45 and 48 years respectively showed a similar lining, but the submucous layers contained a much larger proportion of glandular tissue.

Graham [17] also reports 2 cases of exstrophy of the bladder complicated by adenocarcinoma. He states that the adenomatous tissue in the ectopic bladder is of a precancerous nature and the bladder must be removed. The growth remains locally malignant until well advanced, and metastatic growths are rare. The operation of choice is excision of the bladder preceded or followed by transplantation of the ureters into the rectum.

Kreutzmann [18] reports a case of primary lymphosarcoma of the bladder and states that it is a rare condition, only 4 cases having been reported. He expresses the belief that lymphosarcoma originates from the lymphoid tissue in a chronically irritated bladder. Lymphosarcoma of the bladder is a localized condition without evidence of generalized glandular enlargement. Early diagnosis and radical excision will give the most favorable results.

Wheelock [19] reports 5 cases of sarcoma of the urinary bladder. The diagnoses in all cases were proved by histologic examination. All patients died and 4 postmortem examinations were performed. Two of the 5 patients were women and 3 were men. All were more than 50 years of age. The sarcoma in all 5 cases originated in the lower half of the bladder. Similarly, there was more extensive involvement of the posterior than of the anterior portion of the bladder.

In the gross, the tumors were everting growths at the same time that they infiltrated the walls. Two invaded extravesical tissues. In the 3 cases in which resection was tried there was rapid recurrence. Response to irradiation was unsatisfactory.

In these cases the courses were unusually rapid; the longest was eighteen and the shortest five months. All the patients consulted physicians because of bleeding with other associated symptoms of disease of the lower part of the urinary tract. In the 4 cases in which necropsy was performed, some form of cystitis or pyelonephritis was present and death was attributed to renal insufficiency. No metastasis was found. There was invasion of the perivesical tissues in 1 and of the prostate gland in another.

In brief, additional information derived from a study of the data of investigators is as follows: Nonepithelial tumors of the bladder are infrequently encountered, and of these sarcoma is most rare. The lesion is seen most frequently in the young and next in the old. Sarcomatous tumors of the bladder select the trigone and base. Grossly, they are single or multiple, sessile or pendunculated, soft and friable, usually large, often ulcerated, rapidly growing and invasive. They metas-

18. Kreutzmann, H. A. R.: Primary Lymphosarcoma of the Bladder, J. Urol. **48**:147-152 (Aug.) 1942.

19. Wheelock, M. C.: Sarcoma of the Urinary Bladder, J. Urol. **48**:628-634 (Dec.) 1942.

tasize in 23 per cent of the cases, usually to the liver, the inguinal and regional lymph nodes and the lungs. They are nearly always fatal. Although intimate relation of tumor cells to blood vessels has been noted often, actual invasion and vascular dissemination are uncommon. Death results from obstruction, ascending infection to the kidneys and renal insufficiency.

Buschke and Cantril [20] report 52 cases in which advanced carcinoma of the bladder was treated between 1934 and 1940 with 800 kilovolt roentgen irradiation. All controlled cases in this series were cases of papillary carcinomas without infiltration of the musculature of the bladder. Extensive papillary growths in which infiltration cannot be demonstrated are the most suitable for roentgen therapy. The majority of the patients had been received after one or more unsuccessful fulgurations for papillary carcinomas. The single papilloma of the bladder can be destroyed by fulguration. It is, however, the experience of every urologist that these isolated papillomas tend to recur in other areas of the bladder and from the clinical point of view they are papillary carcinomas rather than papillomas. In certain of Buschke and Cantril's cases in which the papillary growths had recurred after repeated fulgurations roentgen therapy had arrested this process. They therefore feel that those papillary carcinomas of the bladder which either tend to recur or have recurred after one fulguration should be treated with roentgen rays without further delay if this type of treatment is considered at all.

In none of Buschke and Cantril's cases of infiltration of the tumor into the muscle was sterilization performed, regardless of whether the lesions were originally papillary growths with secondary invasion or primarily infiltrating tumors.

External roentgen therapy of the type described for carcinoma of the bladder is a formidable undertaking. It can be conducted with any hope of success only in cases in which the general condition of the patient will support such a major procedure. Good general condition, adequate drainage from the bladder, adequate capacity and absence of extensive infection are prerequisites for a fair trial of this method. A previous suprapubic operation, particularly in the presence of any obstruction or infection, is an additional hazard to intense irradiation. This is not a procedure suitable for palliative purposes only. Patients who have lesions inoperable because of extravesical extension have not been benefited.

Atkinson [21] discusses metastasis to the skin from tumors of the bladder. This type of metastasis is comparatively rare, only a few cases having been reported. Atkinson records the case of a 59 year old man who had a tumor about 2.5 cm. in diameter in the bladder. Grossly the tumor was a papilloma; histologically it was diagnosed as papillary carcinoma. Six weeks later a small nodule appeared on the patient's upper lip. Biopsy showed this to be similar to the growth in the bladder.

Glandular Proliferation.—Emmett and McDonald [22] report 9 cases of proliferation of glands of the urinary bladder simulating malignant neoplasm. All of the 9 patients except 1 complained of varying degrees of dysuria; all except 1 had suffered from hematuria. Urinary infection was present in all but 1 case, while

20. Buschke, F., and Cantril, S. T.: Roentgentherapy of Carcinoma of Urinary Bladder: An Analysis of Fifty-Two Patients Treated with Eight Hundred K. V. Roentgentherapy, J. Urol. **48**:368-383 (Oct.) 1942.

21. Atkinson, R. C.: Skin Metastases from Bladder Tumors, J. Urol. **48**:350-356 (Oct.) 1942.

22. Emmett, J. L., and McDonald, J. R.: Proliferation of Glands of the Urinary Bladder Simulating Malignant Neoplasm, J. Urol. **48**:257-265 (Sept.) 1942.

leukoplakia and vesical calculus each were present in 1 case. In all but 2 cases the cystoscopic appearance of the bladder suggested the presence of a malignant tumor.

Histologically, two distinct types of glands were present. In one type, termed "intestinal type of glands," the acini were lined by a simple layer of columnar epithelium indistinguishable from the goblet cells of the intestinal tract. In the other type, termed "glands of subtrigonal type," the acini were lined by multiple layers of cells, consisting of a single layer of columnar cells adjacent to the lumen of the gland which was surrounded by several layers of stratified squamous epithelium. The latter type is often referred to as the "glands of Albarran." Mucus was demonstrated in both types of glands. Various stages of cystic formation were found in the subtrigonal type. Evidence of inflammatory cells was found in nearly every instance. Emmett and McDonald could not see any similarity between subtrigonal and prostatic glands. In nearly all of their cases the lesions involved the trigone or base of the bladder. They believe that these glands are formed by metaplasia from the epithelial lining of the urinary bladder and may proliferate when associated with inflammation.

Most of their patients responded to treatment consisting of vesical lavage, urinary antiseptics and fulguration.

Embryology of the Muscle of the Vesical Neck.—Trabucco,[23] in discussing the embryology of the muscle of the vesical neck, states that the lower lip of the vesical neck is of mesenchymatous origin. Its development bears no relation to that of the embryonic entodermic sheet. In the rabbit embryo of 18 days, the mesoblastic cellular tissue begins to differentiate into smooth muscle. In the rabbit fetus of 27 days there is a true small muscle with all the adult characteristics. In the smallest human embryo, 8 mm. long, some orientation of the mesenchymatous cells is already noticeable. In the 12 mm. human embryo the mesenchymatous cells tend to be transversally placed before the opening of the wolffian ducts. In the 20 mm. human embryo, the thickening of the area studied is more marked. In the 30 mm. human embryo transverse orientation of the cells in a small cellular band is observed. In the 35 mm. human embryo this band is 60 microns thick. Transformation of the cells that will constitute the muscle of the vesical neck into smooth muscle fibers begins in the 52 mm. human embryo. In the 8 cm. human fetus a true small muscle is apparent. In the human fetus of 4 months the muscle of the lower lip of the vesical neck is clearly differentiated. In a full term human fetus the muscle proper of the vesical neck is perfectly well differentiated, having all the adult characteristics.

PROSTATE GLAND

Carcinoma.—Alyea and Henderson [24] during the past year treated 40 patients with carcinoma of the prostate by castration. A follow-up study in all but 1 case showed a low mortality rate. The immediate clinical results in all cases were most encouraging. One patient had a relapse and extension of the tumor after eight months of comfort.

The subjective signs of improvement after castration are increase in appetite, well-being and energy, relief of metastatic pain, relief of urinary obstruction, disappearance of infection and stopping of recurrent hemorrhage.

Objective clinical and laboratory signs of improvement and regression of the tumor after castration are lowering of the serum "acid" phosphatase, roentgeno-

23. Trabucco, A.: Embryology of the Vesical Neck Muscle, J. Urol. **48**:153-162 (Aug.) 1942.

24. Alyea, E. P., and Henderson, A. F.: Carcinoma of the Prostate: Immediate Response to Bilateral Orchiectomy; Clinical and X-Ray Evidence, J. A. M. A. **120**:1099-1102 (Dec. 5) 1942.

graphic signs of bone healing at the site of the metastatic lesion and disappearance of pulmonary metastatic lesions.

Diethylstilbestrol causes a response similar to castration but not of the same degree. Alyea and Henderson favor castration first and reserve treatment with diethylstilbestrol for patients who show evidence of extragonadal hormone activity or refuse castration.

Creevy [25] states that the number of cases of carcinoma of the prostate gland is increasing, not because of increased individual susceptibility but because of increasing longevity. Its prognosis is poor. The early lesion can be recognized if every small hard nodule in the prostate is subjected to careful study, including biopsy. Aspiration biopsy is least useful when most needed; that is, for small nodules of doubtful character. Treatment may be symptomatic, but radical perineal prostatectomy alone offers any real hope of cure, although its rate of applicability is low. Creevy is of the opinion that widespread trial of radical perineal prostatectomy should be made in properly selected early cases.

Nesbit and Cummings [26] report a series of 75 cases of prostatic carcinoma treated by orchiectomy in which the patients were observed for at least six months. Elevation in the serum "acid" phosphatase was observed in 39 per cent of the cases. Favorable response, as determined by both subjective and objective criteria, was observed in 73 per cent of cases.

There were 20 failures. Four patients died of carcinoma and 1 from congestive heart failure and infection. For 15 living patients the treatment is considered to have failed; 5 showed no favorable response at any time following operation, while the results for 10 are considered delayed failures because they enjoyed freedom from all subjective evidences of their disease for periods of three to twenty-two months after gonadectomy before symptoms recurred.

Nesbit and Cummings observed no satisfactory criteria for prognosticating the results of orchiectomy for carcinoma of the prostate. The occurrence of 10 delayed failures in this series of cases, with postoperative relapse at periods of from three to twenty-two months, offers disquieting implications regarding the ultimate outcome in any case. Regardless of these implications or of the possibility of failure in some cases, it is evident that gonadectomy is a worth while procedure for advanced prostatic cancer and should be recommended when the diagnosis is established.

Gutman,[27] in discussing the finding of serum "acid" phosphatase in cases of carcinoma of the prostate gland, states that it occurs in and is apparently elaborated by the acinar epithelium of the prostate gland. The concentration of the enzyme in prostatic tissue of adult human beings is extraordinarily high (500 to 2,500 units of activity per gram of fresh tissue), many hundred times that of any phosphatase in kidney, liver, duodenal mucosa or bone. The enzyme does not appear in appreciable amount in prostatic tissue of human beings or monkeys until puberty. Prostatic "acid" phosphatase normally is excreted as a constituent of the prostatic fluid; high concentrations are present in seminal plasma of human beings.

Apart from occasional highly undifferentiated prostatic tumors which do not elaborate the enzyme, carcinomatous prostatic tissue contains large amounts of "acid" phosphatase. This holds not only for tumor tissue at the primary site

25. Creevy, C. D.: The Diagnosis and Treatment of Early Carcinoma of the Prostate, J. A. M. A. **120**:1102-1105 (Dec. 5) 1942.

26. Nesbit, R. M., and Cummings, R. H.: Prostatic Carcinoma Treated by Orchiectomy: A Preliminary Report Based on Seventy-Five Cases Observed for at Least Six Months Following Operation, J. A. M. A. **120**:1109-1111 (Dec. 5) 1942.

27. Gutman, A. B.: Serum "Acid" Phosphatase in Patients with Carcinoma of the Prostate Gland: Present Status, J. A. M. A. **120**:1112-1116 (Dec. 5) 1942.

but also for distant metastatic processes. The presence of so much "acid" phosphatase in metastatic lesions secondary to prostatic carcinoma may have some causal relation to the osteoplastic character of most such metastatic lesions in bone.

When carcinoma of the prostate gland metastasizes, invasion of lymph or blood channels is accompanied by escape of the prostatic secretion into the circulation. Because of its high "acid" phosphatase content, prostatic secretion present in blood can readily be detected by means of appropriate chemical methods for estimating the "acid" phosphatase activity of blood serum, which is increased by influx of the prostatic enzyme. This forms the theoretic basis for the now widely used determination of serum "acid" phosphatase in the differential diagnosis of metastasizing prostatic carcinoma.

The effect of castration and estrogens in cases of metastatic prostatic carcinoma constitutes what is perhaps the most rigorous proof yet submitted that malignancy is not necessarily the result of an irreversible urge to grow intrinsic to the tumor cell but may be due in part to stimulation by extrinsic (in this instance endocrine) agents which are subject to some measure of therapeutic control.

Elevated values were obtained in about 85 per cent of a total of 177 cases of proved or suspected metastasis from prostatic carcinoma. About 90 per cent of patients with carcinoma of the prostate but without roentgenographic evidence of involvement of bone gave values consistently less than 3 units, as did all normal subjects, all patients with prostatic disease other than carcinoma and more than 90 per cent of a total of 853 patients with nonprostatic disease. Falsely high serum "acid" phosphatase values occurring in cases of diseases other than prostatic carcinoma with metastasis most commonly result from the use of hemolyzed serums.

There is no correlation between the levels of "acid" and "alkaline" phosphatase in the serum in cases of prostatic carcinoma except that the concentration of both is normal before dissemination of the tumor and usually above the normal maximum after metastatic spread has occurred. The increase in serum "alkaline" phosphatase is of osseous origin and reflects the extent and vigor of the osteoplastic reaction of bone at the site of the skeletal metastatic processes; if the liver also is involved, a further increase in serum "alkaline" phosphatase may result from obstruction to excretion of the enzyme in the bile.

The method is incapable of detecting prostatic carcinoma which has not yet metastasized and is therefore of no value in the important problem of differentiating that condition from benign prostatic hypertrophy.

Only meager data are available regarding the effect of estrogens on the serum phosphatases in cases of metastatic spread of carcinoma of the prostate. These make it clear, however, that estrogens in appropriate dosage generally cause a fall in serum "acid" phosphatase and a delayed rise in serum "alkaline" phosphatase.

Herbst [28] states that the biochemical control of carcinoma of the prostate gland is based on the principle of the maintenance of low levels of androgen and "acid" phosphatase in the blood. Testosterone elevates blood phosphatase and therefore should be administered with caution to men. The dose of estrogens to be administered should not be more than that required to maintain control of the malignant process, which is a variable and indivdiual quantity. In some instances the malignant process may be accelerated rather than controlled by diethylstilbestrol. Should the prostatic carcinoma of patients who have been castrated cease to remain latent, as has occurred in carcinoma of the breast following bilateral oophorectomy, it would seem likely that additional control may be maintained by

28. Herbst, W. P.: Biochemical Therapeusis in Carcinoma of the Prostate Gland, J. A. M. A. **120**:1116-1120 (Dec. 5) 1942.

giving estradiol dipropionate or diethylstilbestrol and possibly other biochemical agents not yet utilized or available. These relatively simple methods of biochemical control of prostatic carcinoma should have a wide field of application even though the control cannot be maintained indefinitely. The relief of pain alone more than justifies their use.

Bumpus [29] is of the opinion that the proof of the greatest good done to the greatest number of patients with carcinoma of the prostate rests with the advocates of radical surgical removal, who as yet have not published lists of survivals in sufficient numbers to be convincing, when their records are compared with equal numbers of patients simply relieved of their obstructions. Now Thompson has come forward with a report that seems to Bumpus to make the position of the advocates of radical operation still more untenable. Thompson showed that after transurethral resection in a series of patients sufficiently large to be convincing statistically, with a mortality of only 1 per cent, 14 per cent lived more than five years. Now that estrogens and castration are available to aid in the treatment of these men, Bumpus predicts that prolonged survivals will be so numerous as to make even the consideration of cure by radical removal with the possibility of mortality and lifelong incontinence seem indeed fantastic. There can be no question about the prolongation of life following castration.

Kearns [30] has a series of 42 cases of carcinoma of the prostate, in about 70 per cent of which varying degrees of benefit occurred. All of the results were obtained through the use of estrogens alone. First he used diethylstilbestrol; later ethinylestradiol was used by mouth; still later subcutaneous implantation of alpha estradiol was employed. The last named is the preferred method of administration of estrogen. It is especially applicable for patients who are unable to tolerate either diethylstilbestrol or ethinylestradiol by mouth. It may well be combined with the oral administration of diethylstilbestrol or ethinylestradiol. The one route of administration may be employed to augment the other according to clinical indications.

Vermooten [31] reports observations on 58 cases of carcinoma of the prostate gland in which bilateral orchiectomies were done. Six years previous to the writing of the report he performed total radical prostatectomy on an old man for carcinoma. Six months previously this patient returned with extensive skeletal and pulmonary metastatic processes but without local recurrence. Before orchiectomy he was extremely dyspneic and practically moribund. Vermooten reports that this patient is once more completely free from metastatic lesions. This makes Vermooten wonder whether radical prostatectomy for even an early lesion is really worth while.

Creevy [32] emphasizes the fact that he has advocated radical operation only in the earliest stages. During the period under discussion only 10 radical perineal prostatectomies have been done at the University Hospital (Minneapolis) in a

29. Bumpus, H. C., Jr., in discussion on papers of Alyea and Henderson,[24] Creevy,[25] Thompson,[42] Nesbit and Cummings,[26] Gutman [27] and Herbst,[28] J. A. M. A. **120**:1120 (Dec. 5) 1942.

30. Kearns, W. M., in discussion on papers of Alyea and Henderson,[24] Creevy,[25] Thompson,[42] Nesbit and Cummings,[26] Gutman [27] and Herbst,[28] J. A. M. A. **120**:1121 (Dec. 5) 1942.

31. Vermooten, V., in discussion on papers of Alyea and Henderson,[24] Creevy,[25] Thompson,[42] Nesbit and Cummings,[26] Gutman [27] and Herbst,[28] J. A. M. A. **120**:1121 (Dec. 5) 1942.

32. Creevy, C. D., in discussion on papers of Alyea and Henderson,[24] Creevy,[25] Thompson,[42] Nesbit and Cummings,[26] Gutman [27] and Herbst,[28] J. A. M. A. **120**:1122 (Dec. 5) 1942.

group of about 500 cases of carcinoma of the prostate gland. All of the patients who had any important obstruction to urination, except for the 10 included in the report, were treated by transurethral resection with or without irradiation. Creevy raises the question as to whether it is justifiable to attempt to cure any sort of cancer of any organ. He does not believe that the general surgeons, despite the low percentages of cures in carcinoma of the stomach or rectum, will concede that one ought to give up, and he still thinks that it is worth while to try for a cure in an appropriate case of early carcinoma of the prostate. He is inclined to hold to that point of view because it will not be known for a long period whether relief from castration or from the estrogens can be counted on. If it is going to be just a flash in the pan, as was castration for inoperable carcinoma of the breast, then Creevy thinks that the availability of the hormone preparations is not a serious argument against radical perineal prostatectomy.

Chute, Willetts and Gens [33] state that reducing the action of androgens in the body was of benefit in 26 of 27 cases of inoperable carcinoma of the prostate gland. The action of androgens was reduced by surgical castration, by biochemical neutralization, by the administration of the synthetic estrogen stilbestrol or by a combination of the two; the last method was used in a majority of the cases (77 per cent).

Beneficial effects in these cases included rapid relief from the pain of metastatic lesions if present, great improvement in appetite and general health with gain in weight and reduction in the size and induration of the prostate with improvement in ability to urinate in most cases.

The injection of 10 mg. of diethylstilbestrol per day for five to ten days augmented the beneficial effects of castration noticeably and rapidly. Similar injections of diethylstilbestrol without castration gave equally noticeable and rapid effects, but these disappeared when its administration was discontinued, whereas the effects of castration, while slower to appear, were permanent. If diethylstilbestrol alone is used, patients have to be given a small oral maintenance dose indefinitely (1 to 3 mg. per day).

Chute, Willetts and Gens feel that the quickest and most satisfactory results in this series were obtained by castration followed by the injection of 10 mg. of diethylstilbestrol per day for five to ten days. Thirteen patients who were suffering from moderate or marked difficulty of urination were treated in this way. The size of the obstructing prostate gland was so reduced in 9 cases that the patients could void freely, did not have much residual urine and escaped having to undergo an operation for the relief of prostatic obstruction. Chute, Willetts and Gens recommend this type of treatment.

No serious harmful effects were noted from the injection of 10 mg. of diethylstilbestrol per day for five to ten days, or from the oral ingestion of 2 to 3 mg. per day over a period of nine months. Unpleasant side effects of treatment with this compound were loss of libido and power of erection, tenderness and hypertrophy of the nipples and breasts, atrophy of the testes and anorexia or occasionally nausea. After castration, libido and power of erection usually disappeared, but there were no other harmful effects.

No beneficial effect was noted on metastatic growths in bone. Roentgenograms taken over a period of more than six months showed them apparently progressing as usual.

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33. Chute, R.; Willetts, A. T., and Gens, J. P.: Experiences in the Treatment of Carcinoma of the Prostate with Stilbestrol and with Castration by the Technique of Intra-Capsular Orchidectomy, J. Urol. **48**:682-692 (Dec.) 1942.

As found by other authors, the concentration of "acid" phosphatase, if elevated, fell rapidly toward normal following castration or administration of diethylstilbestrol, whereas the value for "alkaline" phosphatase usually rose.

Neuswanger [34] reported 57 cases of carcinoma of the prostate gland in which treatment consisted of castration and 11 others in which diethylstilbestrol was employed. It has been his experience that the carcinomatous gland recedes in about three to five weeks after operation but that the extracapsular metastatic lesions are affected little or not at all, at least up to the period of twelve months during which time his patients had been under observation.

An interesting result encountered was that of incontinence, which was noticed in 2 cases after castration alone. It is possible that this can be explained by the fact that the sphincter muscle has been weakened by the invasion of the carcinoma and castration causes relaxation and incontinence of urine.

In 1941 Baron and Angrist reported a 10 per cent incidence of occult carcinoma in 364 cases in which random sections of the prostatic tissue were examined at necropsy. In 46 per cent of 50 cases in which a complete study of the gland was done at necropsy following death from causes other than carcinoma of the prostate, they found occult carcinoma.

The untoward results encountered consisted of swelling of the ankles, hot flushes, loss of sexual capacity and tender enlargement of the breasts. The favorable symptoms encountered, which far outweigh the undesirable results, included relief of pain, increase in appetite, gain in strength and weight, improvement in bowel habits and decrease in obstructive symptoms.

Herbst,[35] in discussing carcinoma of the prostate gland, states that his observations in twenty-two months' experience have been the same as those just reported except that he employed a smaller dose of estrogen. The reactions observed in the breast have varied from no response at all to gynecomastia (interestingly, in 2 instances unilateral gynecomastia). Estradiol dipropionate was the first estrogenic substance which Herbst used. He has not been able to observe any difference in the response to the administration of estradiol dipropionate and diethylstilbestrol. He states that the only difference so far demonstrated between these substances is the fact that diethylstilbestrol in huge doses is slightly more effective in producing anesthesia in rats than is estradiol.

As time goes on and clinical observations accumulate, certain differences may be recognized in these substances which at present are not apparent. An interesting observation was made on a patient with diabetes who was requiring 12 mg. of protamine zinc insulin daily while being treated with diethylstilbestrol. Since castration, which was done six months previously, he had not required any insulin.

In a microscopic study no changes in cell morphology were observed in 3 instances in which it was possible to study malignant tissue after castration, the administration of diethylstilbestrol, or both. This observation makes it seem unlikely that ordinary microscopic studies will be of much value and that such stains as the Gomori stain will have to be developed so that observations of practical significance may be demonstrated.

The dosage employed in the administration of estradiol dipropionate and diethylstilbestrol was 1 mg. three times a week hypodermically. Recently Herbst has thought that increasing the dose is justifiable and indicated when satisfactory response is not experienced with the 1 mg. dose.

34. Neuswanger, C. H., in discussion on papers of Alyea and Henderson and Chute, Willetts and Gens,[33] J. Urol. **48**:694-697 (Dec.) 1942.

35. Herbst, W. P., in discussion on papers of Alyea and Henderson and Chute, Willetts and Gens,[33] J. Urol. **48**:697-698 (Dec.) 1942.

Dean [36] states that while the final explanation of the cause and prevention of prostatic cancers, if not their cure, will be produced in the chemical laboratory, a prominent part must be played by the urologist, who is a trained observer of the reactions of the test object, the patient. In a group of 40 patients, 15 with metastasis, Alyea found 4 with metastatic lesions in the lung which responded as do secondary deposits in the soft parts elsewhere in the body. In the 60 patients Dean has treated in the past eleven months, no metastasis to the lungs was discovered. After treatment, it is his impression that the patients of Alyea and of Chute and his associates responded in the same spectacular way that so many observed patients have. However, Dean admits that the early benefits of castration were not sustained by as high a proportion of his patients, the majority of whom relapsed after five to six months, nor could he detect as much regression of the primary prostatic tumor and reduction of residual urine after orchiectomy, although the administration of diethylstilbestrol in daily doses of from 3 to 5 mg. produced striking improvement in these respects.

In Dean's experience, after castration the androgen output rose an average of 45 per cent in two thirds of the patients. Assays for estrogen showed decreased excretion in every case. If these analyses represent the true condition of these men, castration should have made them worse, because it appeared to increase markedly their production of androgens relative to estrogens.

Munger,[37] in discussing carcinoma of the prostate gland, defends his premise enunciated first in 1934 and again established in a follow-up report presented at Colorado Springs before the American Urological Association in 1941, namely, that carcinoma of the prostate is in some manner related to production of the testicular hormone and that well directed, well planned and properly instituted roentgen therapy applied directly to the testicles will definitely influence that carcinogenic substance, whatever it is, which apparently has its origin in the testicle and seems to be related to carcinoma of the prostate.

The paper presented in Colorado Springs in 1941 was entirely a clinical summation of the procedure as it had been carried on since 1932. After this clinical presentation Munger was rebuffed by certain roentgenologists, pathologists and urologists, whose chief counterargument was that "testicular irradiation has no effect upon the interstitial cells." Munger adds that he is not in a position as yet to state how much organic effect irradiation has on the interstitial cell of the testis, but he says with certainty that if the interstitial cells are the station from which emanates that factor responsible or related to the establishment of carcinoma of the prostate, then roentgen rays do have some effect, basically at least, on the functioning of the interstitial cells. Surgical castration certainly removes the testicle, and thereby the carcinogenic factor within the testicle; diethylstilbestrol does definitely depress this factor within the testicle, and in 85 per cent of cases irradiation seemingly stabilizes or reverses the process. Munger believes all the factors involved are not yet disclosed and that the biochemists may find the answer to this problem.

Sullivan, Gutman and Gutman [38] review the theoretic and experimental developments leading to the use of the determination of serum "acid" phosphatase in cases of metastasizing prostatic carcinoma.

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36. Dean, A. L., in discussion on papers of Alyea and Henderson and Chute, Willetts and Gens,[33] J. Urol. **48**:698-699 (Dec.) 1942.

37. Munger, A. D., in discussion on papers of Alyea and Henderson and Chute, Willetts and Gens,[33] J. Urol. **48**:701-702 (Dec.) 1942.

38. Sullivan, T. J.; Gutman, E. B., and Gutman, A. B.: Theory and Application of the Serum "Acid" Phosphatase Determination in Metastasizing Prostatic Carcinoma: Early Effects on Castration, J. Urol. **48**:426-458 (Oct.) 1942.

The reliability of the determination as a practical method for the diagnosis of metastasizing prostatic carcinoma is considered on the basis of results obtained in a period of four and a half years of clinical trial. The method failed; that is, values less than 3 units per hundred cubic centimeters were obtained in approximately 15 per cent of 130 cases of prostatic carcinoma and definite or suggestive roentgenographic evidence of metastasis; in the remaining 85 per cent of cases increases in serum "acid" phosphatase occurred, which in extreme instances exceeded 1,000 units per hundred cubic centimeters. Values of less than 3 units per hundred cubic centimeters were obtained in approximately 89 per cent of 70 cases of prostatic carcinoma without roentgenographic evidence of skeletal metastasis, as well as in all of 85 cases of diseases of the prostate gland other than carcinoma. The conclusion drawn from this experience is that the method is consistent and specific enough to be a valuable, though not infallible, supplement to clinical, roentgenographic and other procedures for the diagnosis of metastasizing carcinoma of the prostate gland.

The applications of the determination which have proved useful in diagnosis and treatment are discussed. They include: (1) corroborating the diagnosis of metastasizing prostatic carcinoma when suggested by other methods; (2) providing evidence of metastasis from prostatic carcinoma before it is definitely demonstrable by roentgenologic or other methods; (3) determining the prostatic or nonprostatic origin of tumors in cases of known metastasis; (4) differentiating Paget's disease from metastatic prostatic carcinoma; (5) aiding in the selection of cases for prostatectomy and in the detection of recurrence after prostatectomy, and (6) aiding in the selection of cases in which the disease could be controlled with androgen and in the evaluation and regulation of such treatment. Cases are cited to illustrate these applications.

Castration in 31 cases of metastasizing prostatic carcinoma and serum "acid" phosphatase levels ranging from 520 to 4.2 units per hundred cubic centimeters resulted in an early precipitous fall in serum "acid" phosphatase (often temporarily arrested about the third week by a slight, transient secondary rise, to be followed by a prolonged decline) until at the end of two or three months an equilibrium was reached. The effect of castration on the serum "alkaline" phosphatase was more variable. After a latent period a marked increase in serum "alkaline" phosphatase usually developed, most often about the second or third week, followed by a gradual decline until equilibrium was reached after many months.

Hamm [39] states that cancer of the prostate gland is one of the most common forms of cancer. It occurs three times as often in the prostate gland as in any other internal organ in man. Of 316 of Hamm's patients coming to operation for various types of urinary obstruction, 38 (about 12 per cent) had carcinoma.

Adenocarcinoma is the type of cancer most frequently found. In more than half of the cases it is seen in combination with adenomatous hyperplasia, although there is no evidence that the two processes are related. The adenomatous and carcinomatous portions usually overlap.

In some instances metastasis may be extensive even before the neoplasm can be detected by gross inspection of the specimen at necropsy. The most common sites of metastasis are the pelvic girdle and the lumbar vertebrae. Metastasis to bone is predominantly of the osteoplastic type, especially when widespread. When a metastatic lesion of the osteoplastic or mixed type involving the bony pelvis or lumbar vertebrae is found, it is in all probability due to carcinoma of the prostate. In 18 (47.1 per cent) of the 38 operative cases in this study, roentgenographic evidence of metastasis was present at the time of operation.

39. Hamm, F. C.: Clinical Aspects of Carcinoma of the Prostate: Review of Thirty-Eight Operative Cases, J. Urol. **48**:174-186 (Aug.) 1942.

Advanced carcinoma is characterized by its stony hardness, nodules and a general sensation of being fixed in the pelvis. It is difficult to outline the gland, because its borders seem to merge with the surrounding pelvic structures. There is an obliteration of the median sulcus; the superior margin of the gland may have a shelflike feel so that the examining finger can be hooked over it.

In 6 (15.7 per cent) of Hamm's 38 operative cases there had been no follow-up since operation. Nine patients (23.6 per cent) were traced from three months to three years, but had been lost track of. Fifteen patients (39.5 per cent) were known to be dead. Eight patients (21.05 per cent) have been followed from the date of operation to the present time. Seven of the 8 patients are in excellent health. The ninth patient, who has survived the longest period (five years and eight months) is not well. He has pain extending to the penis and has been advised to undergo orchiectomy.

Riba [40] discusses subcapsular castration for carcinoma of the prostate gland. The anterior scrotal wall is blocked off with 1 per cent procaine hydrochloride solution. Ten cubic centimeters is then injected directly into each spermatic cord. Each testis may be delivered easily through a 4 to 5 cm. median incision. On the anterior surface both the tunica vaginalis and the tunica albuginea are widely incised. The exposed parenchyma can be easily removed en masse by blunt dissection. The bleeding is minimal. Active bleeders are ligated. Both tunicae are resutured with fine silk. The testis is returned to its bed. The opposite testis is treated likewise through the same incision. The edges of the wound are approximated with interrupted silk sutures or skin clips. The mild intracapsular hemorrhage causes the tunicae to become distended and remain firm, in some instances for many months. The patient is unaware that the total parenchyma is absent. Postoperative mental discomfort is minimized or absent.

Randall [41] reports the results in 5 cases from seven to nine years after castration for carcinoma of the prostate gland. In none of these cases was the malignant process cured. On the other hand, all 5 patients had advanced carcinoma and probably metastasis, and Randall states that failure to obtain a cure may be related to this fact.

Thompson [42] states that carcinoma of the prostate gland is an insidious disease which usually does not cause symptoms until it is well advanced. It is difficult to detect in its early stages by any known clinical method.

In 95 per cent of cases the disease has spread beyond the confines of the prostate gland when the patients are first observed; in 5 per cent or less, radical perineal prostatectomy may be justified as a method giving hope of cure in the strict sense of the word.

Transurethral resection is the most desirable operation for the relief of obstructive urinary symptoms caused by the disease. Entirely adequate relief for prolonged intervals follows if the operation is properly performed. Normal vesical function is achieved at minimal risk to life and practically no risk of incontinence will result.

Transurethral resection of the obstructing tissue combined with bilateral orchiectomy as suggested by Huggins and the administration of diethylstilbestrol seem to constitute the best method of treatment now available for patients who have reten-

40. Riba, L. W.: Subcapsular Castration for Carcinoma of Prostate, J. Urol. **48**:384-387 (Oct.) 1942.

41. Randall, A.: Eight-Year Results of Castration for Cancer of the Prostate, J. Urol. **48**:706-709 (Dec.) 1942.

42. Thompson, G. J.: Transurethral Resection of Malignant Lesions of the Prostate Gland, J. A. M. A. **120**:1105-1109 (Dec. 5) 1942.

tion of urine. Unless urinary obstruction exists, orchiectomy and diethylstilbestrol therapy seem to constitute the treatment of choice.

Hypertrophy.—Davis,[43] in discussing the renaissance of prostatectomy with particular reference to minimal hospitalization without preliminary drainage, states that the urologic surgeon now sees a much larger percentage of "conspicuously good risks," permitting safe prostatic surgery without preliminary drainage. Results obtained in a consecutive series of 24 such cases indicate that the average total period of preoperative and postoperative hospitalization, with good risks, may be reduced to a figure not exceeding sixteen days. This exceedingly short average total hospitalization for perineal prostatectomy tends to nullify the chief argument of those advocating routine or indiscriminate transurethral resection rather than selection of cases. Davis states that this opinion should not be interpreted as blanket approval of prostatectomy without preliminary drainage, the necessity of which will always obtain in cases of impairment of renal function.

Humphreys [44] reviews the causes of unsatisfactory end results after prostatectomy. After examining the follow-up records of the last 500 prostatectomies in the Cornell Urological Service of the New York Hospital, he found four main causes of unsatisfactory results for which patients had to return for reoperation after prostatectomy in cases in which results still appeared satisfactory six months after operation. The cases were grouped according to these causes.

The commonest cause of poor postoperative results after uncomplicated prostatectomy is persistent urinary infection. In Humphreys' series there were 2 instances of the formation of stones in infected bladders, despite the fact that there was no residual urine. These persistent infections may become less frequent with the advent of the use of sulfonamide compounds. Infections are now being treated routinely with the sulfonamide derivatives and fewer persistent infections are being encountered. If adequate chemotherapy and better follow-up care had been given these two patients, dysuria and formation of stones might have been prevented.

A second cause of unsatisfactory end results after prostatectomy is obstruction of the neck of the bladder due to the formation of scars. Some patients showed delayed healing of urinary sinuses immediately after prostatectomy, owing to the early appearance of scars in the region of the neck of the bladder. They were relieved by transurethral resection. Three of Humphreys' patients and 4 others who had seemingly satisfactory prostatectomies performed elsewhere returned with urinary difficulties due to scars in the form of partial diaphragms at the neck of the bladder. These patients were relieved of their obstructive symptoms by transurethral resection after the vesical neck had been dilated with bougies.

A third cause of unsatisfactory end results after adequate prostatectomy is true recurrence of prostatic hypertrophy. In spite of the difficulties of removing completely all hypertrophic prostatic tissue at operation and in spite of the possibilities of recurrent growth in glandular tubules which remain in the prostatic tissue left, the number of operations for recurrent hypertrophy of prostate glands is small.

Only 2 patients in Humphreys' series of 500 patients operated on for supposedly benign prostatic obstruction returned for subsequent operation because of urinary difficulties resulting from carcinoma of the prostate. Since in both cases treatment for prostatic hypertrophy antedated the second admissions by only three years, it may be assumed that carcinoma of the prostate had been

43. Davis, E.: The Renaissance of Prostatectomy with Particular Reference to Minimal Hospitalization Without Preliminary Drainage, J. Urol. **48**:163-169 (Aug.) 1942.

44. Humphreys, G. A.: Some Causes of Unsatisfactory End Results After Prostatectomy, J. Urol. **48**:388-391 (Oct.) 1942.

present at the time of the first operations; however, if so, in each case the carcinoma was masked by the symptoms of hypertrophy, the patient was relieved by the removal of the hypertrophied gland and the sections of tissue removed showed no carcinoma.

Female Prostate.—Folsom and O'Brien [45] discuss the female obstructing prostate. They believe that an infection harbored through the years in the glands surrounding the posterior urethra is the cause of the pathologic picture seen in this portion of the female urethra. From observations, they are convinced that prostatism is a clinical entity that occurs much more frequently in women than is recognized and properly treated. Physicians have so long considered the female prostate as nonexistent that they often fail to ask the proper questions to get an accurate and revealing history.

Clinically these patients present, in addition to irritation of the bladder, some degree of difficulty in voiding. This varies from simply a sense of obstruction and unfinished business on through varying degrees of obstruction to complete retention. Three out of 15 of Folsom and O'Brien's patients had retention.

In 4 cases the vesical urine showed pus to a degree of 4 plus or more, while the specimens of urine collected from the right and left kidneys showed no pus and no organisms. In each of these cases the mucosa of the bladder was not inflamed. Therefore Folsom and O'Brien feel that the condition in these cases is comparable to a similar one in the male, in which the pus originates in the posterior part of the urethra from the prostate and seeps back into the bladder through the relatively weak internal vesical sphincter. A plain cystogram, made with the use of either air or sodium iodide, will frequently reveal a filling defect in the region of the internal orifice similar to the defects seen in men with prostatic hypertrophy. On cystoscopic examination the vesical wall may be normal or grossly trabeculated with cellules and even diverticula and calculi. In the majority of the cases fibromuscular hypertrophy with fibrous hyperplasia and varying grades of inflammatory reaction are present. In some cases actual gland structures have been reported, and these seem to be identical with similar lesions in the male.

Folsom and O'Brien are of the opinion that the most plausible explanation for the pathologic lesion under discussion is, first, that there is a homologous group of glands surrounding the posterior part of the female urethra and, second, that these glands do become infected and that after they have harbored this infection for months or years bars, collarets and cicatricial contractions are produced.

In performing transurethral resection in the female one must be much more careful in technic than in operating on the male: first, for the simple reason that in dealing with miniature prostates it is necessary to be more sparing in the bites of tissue removed to insure against cutting through the urethrovaginal septum; second, for the reason that there is not, as far as has been observed, a capsule that may be seen during resection and hence act as a guide; third, because excessive fulguration may be as bad as too deep a cut. As little fulguration as possible should be used and the Foley bag and traction should be relied on to control the bleeding.

In 5 of Folsom and O'Brien's cases the resection was limited to the lower segment of the urethral circumference, since they were in these cases dealing with a bar. In 9 cases the entire circumference of the urethra was resected. It was necessary to resect the upper segment in 1 of these cases, in which no result was obtained after the first resection, which was limited to the lower segment.

45. Folsom, A. I., and O'Brien, H. A.: The Female Obstructing Prostate, J. A. M. A. **121**:573-580 (Feb. 20) 1943.

Only 1 death occurred after resection in this series of cases, that of a woman aged 67 years who had rather severe diabetes and myocardial damage resulting from a previous coronary occlusion.

Nesbit [46] states that in the reported cases of prostatism in women in which relief has been brought about by transurethral resection three definite objective findings have been of value in diagnosis: first, residual urine; second, trabeculation of the bladder and, third, a palpable lesion which can be seen with the aid of a cystoscope or a urethroscope. During the past year, Nesbit has seen 2 women whose cases might fall into this category. They had difficulty with urination. One of them had complete retention of the urine requiring catheterization. Neurologic examination gave negative results in both cases. In both there was residual urine. There was a moderate degree of trabeculation, and on pantoscopic examination a visible bar was present which was not palpable by vaginal examination on the instrument. In these 2 cases, it was suspected that neurogenic contraction of the vesical outlet or the internal sphincter might have been present. In order to differentiate this point, a local anesthetic agent was injected into the lumbar sympathetic nerves. One can tell whether this injection is taking hold, because immediately the patient's legs get an increase in warmth. In both cases the visible contracture of the vesical outlet disappeared on cystoscopy, and Nesbit was saved the embarrassment of having operated on a functional rather than an organic bar, which is something to hold in mind. Residual urine, trabeculation of the bladder and a palpable lesion are important.

Kretschmer [47] states that obstruction at the neck of the bladder in both children and adult females is a rare lesion. However, it occurs more frequently than is generally recognized. Many girls and women with trabeculation and hydronephrosis have as the underlying cause obstruction at the neck of the bladder. This condition is frequently overlooked, and as a rule the patients when consulting the physician come in late in the course of the disease, after irreparable damage to the upper part of the urinary tract has occurred. Therefore it behooves all to be on the lookout for such obstruction and to remove it before damage to the upper part of the urinary tract has taken place. Kretschmer agrees with Folsom and O'Brien that the treatment is transurethral resection. He has had most satisfactory results.

O'Conor [48] states that he has encountered 9 women with unmistakable mechanical obstruction of the vesical neck. Folsom and O'Brien have had the opportunity of studying Kodachrome photomicrographs of the tissue removed by transurethral resection from these 9 patients. The obstructing tissues removed from the patients O'Conor has seen has not been uniform. Some of these tissues were purely fibromuscular, some were granulomatous or inflammatory and some had a predominance of glandular elements. O'Conor agrees that the term "prostatism" as applied to women is misleading. Patients with this condition must not be confused with the hermaphrodites or pseudohermaphrodites who actually appear to be female yet have male gonadal tissue. Before resection of an apparent obstruction at the neck of the bladder in women, it is imperative that the part which relaxation of the floor of the bladder plays be recognized. In cystocele, moderate or advanced, cystoscopic examination often reveals an apparent increase in the size of the internal sphincter or vesical neck. The neurologic examination must be negative, there must be both visual and palpable tissue apparently

46. Nesbit, R., in discussion on Folsom and O'Brien.[45]
47. Kretschmer, H. L., in discussion on Folsom and O'Brien.[45]
48. O'Conor, V. J., in discussion on Folsom and O'Brien.[45]

obstructive in character and there must be residual urine that cannot be explained by relaxation of the floor of the bladder before the indications are clear for transurethral resection of the vesical neck of the female.

TESTICLES

Tumor.—Gilbert [49] reviews 60 cases of pseudohermaphroditism with testicular tumors and presents 1 additional case, making a total of 61 cases. This group is approximately 1.0 per cent of 5,516 cases of testicular tumor studied in detail. The pathologic types in the neoplasms studied consisted of 38 unicellular tumors (seminoma; 62.2 per cent); 14 teratomas (22.6 per cent) and 9 miscellaneous or "malignant" tumors (14.7 per cent). Two tumors were located in the scrotal testis, 8 in the inguinally retained testis and 48 in the abdominally retained testis. Neither the side nor the site of the remaining 3 growths was stated in the reports. In 8 cases both gonads were involved. In 41 cases the lesion was considered operable. Operation was performed in 11 cases in spite of metastasis, while the lesions in the remaining 9 were considered inoperable. Four patients survived 5 years or more, 3 of whom had unicellular tumors and 1 a teratoma.

Reports of the 8 cases of bilateral testicular tumor are given in abstract form because of their importance in the study of paired organs. The pathologic types in this group were unicellular tumors in 4 cases, teratomas in 3 and adenoma in 1 case.

In only 4 cases were Aschheim-Zondek assays carried out, and all failed to show the presence of any choriogenic hormone. In all 4 cases unicellular tumors were present. No assays for estrogen or androgen were made.

Three of the 52 noninvolved gonads were located in the scrotum, 1 in the perineum, 8 in the inguinal region and 38 in the abdomen. In 2 instances the site was not stated. Inguinal hernia was present in 12 cases (19.7 per cent). The presence of hernia may be the only lead to the identification of pseudohermaphroditism.

Dockerty and Priestley [50] state that tumors of the testicle are relatively infrequent, occurring only once in approximately every 1,500 males admitted to larger clinics. Ninety-five per cent of these tumors are malignant, with seminoma and carcinomatous teratoma sharing an almost equal incidence. Sarcoma, for some strange reason, is rarely observed in the testis. The authors present the clinical and pathologic data in 4 cases of lymphosarcoma of the testicle. Whereas earlier cases of seminoma had been mistaken for lymphosarcoma, modern cytologic studies combined with a more or less characteristic cellular infiltration about recognizable seminiferous tubules furnished the criteria for accurate differentiation. Involvement of the skin and of lymph nodes was observed and interpreted as evidence that the testicular lesion was metastatic and not primary, since the nodule in the testicle sometimes appeared as a late manifestation. A high incidence of bilateral involvement (50 per cent) was similarly interpreted. The only other metastatic malignant lesion Dockerty and Priestley could find in a series of 400 testicular tumors was a melanoepithelioma. Thus lymphosarcoma of the testicle, however rare, represented the majority of metastatic malignant processes involving the testicle.

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49. Gilbert, J. B.: Studies in Malignant Testis Tumors: VIII. Tumors in Pseudohermaphrodites; Review of Sixty Cases and a Case Report, J. Urol. **48**:665-672 (Dec.) 1942.

50. Dockerty, M. B., and Priestley, J. T.: Lymphosarcoma of the Testis (Report of Four New Cases), J. Urol. **48**:514-523 (Nov.) 1942.

Prince [51] reports 2 cases of rhabdomyosarcoma of the testicle. One of the tumors was a highly undifferentiated growth, without demonstrable elements to prove its teratomatous nature. The other was a fairly well differentiated growth showing, in addition to the predominating rhabdomyosarcoma, areas of embryonal carcinoma, adenocarcinoma and papillary adenocarcinoma, with benign structures derived from all three germ layers.

Dermoid Cysts.—Dockerty and Priestley [52] report 3 cases of dermoid cysts of the testicle. Although primary testicular tumors occur in approximately 1 of every 1,500 males admitted to the Mayo Clinic, dermoid cysts constituted less than 1 per cent of testicular tumors. The tumors reported were slow growing and benign. In 1 case the history indicated a congenital injury. In 1 case stratified squamous cells without any specialized epithelial structures made up the cyst wall, while in 2 cases all three germ layers were represented although ectoderm and its derivatives were predominant. Orchiectomy was performed in all 3 cases.

EPIDIDYMIS

Tumors.—Gordon-Taylor and Ommaney-Davis [53] state that tumors of the epididymis are the least frequent of all neoplasms.

They report a case of adenoma of the epididymis. The patient, a young man, had swelling in the left side of the scrotum. Examination revealed a painless enlargement of the testicle. The epididymis apparently was not selectively involved, and a diagnosis of tumor of the testicle was made. Castration was carried out, and examination revealed an encapsulated, rounded tumor of the epididymis separate from the testicle. Microscopic examination revealed the growth to be an adenoma.

Blumer and Edwards [54] report a case of adenoma of the epididymis. Their patient was a man 54 years of age. He had a hydrocele which had been tapped a year previously. He stated that he had a stone in his scrotum which had been present since he was a boy. A radical operation for hydrocele was performed, and a small, rounded hard mass was discovered in the lower end of the testicle. The mass was removed by blunt dissection; it was completely and easily separated from the testicle and epididymis, which appeared quite healthy, but on histologic examination the lesion was found to be an adenoma of the epididymis.

Strong [55] discusses tumor of the epididymis and reports the case of a man aged 38 years who had a nodule in the region of the right testicle which was noticed first five years before examination. The tumor was about 1 cm. in diameter and caused little trouble. Examination showed the lower pole of the right epididymis to be enlarged, smooth and firm, adherent to the testicle but not to the skin. The proximal 4 to 5 cm. of the vas was somewhat nodular. Epididymectomy and partial vasectomy on the right side, with removal of a small amount of normal testicular tissue, was carried out. Histologic examination revealed the tumor to be a rhabdomyosarcoma. Strong states that this is probably the first recorded instance of such a primary epididymal tumor.

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51. Prince, C. L.: Rhabdomysarcoma of the Testicle, J. Urol. **48**:187-195 (Aug.) 1942.
52. Dockerty, M. B., and Priestley, J. T.: Dermoid Cysts of the Testis, J. Urol. **48**: 392-400 (Oct.) 1942.
53. Gordon-Taylor, G., and Ommaney-Davis, C.: A Case of Adenoma of the Epididymis with a Note on Solid Tumors of the Epididymis, Brit. J. Surg. **29**:260-262 (Oct.) 1941.
54. Blumer, C. E. M., and Edwards, J. L.: Adenoma of the Epididymis, Brit. J. Surg. **29**:263-265 (Oct.) 1941.
55. Strong, G. H.: Primary Malignant Tumor of the Epididymis (Rhabdomyosarcoma), J. Urol. **48**:533-535 (Nov.) 1942.

SPERMATIC CORD

Tumor.—Strong [56] states that involvement of the spermatic cord by neoplasm is an uncommon but not rare occurrence. To date, 257 tumors have been reported, of which 64 per cent were benign. Malignant tumors appearing in the spermatic cord have been predominantly sarcomatous. He records a case of lipomyxoma of the spermatic cord and 5 additional cases of tumors of the spermatic cord.

Marshall [57] reports a case of tumor of the spermatic cord. The patient, a man 62 years of age, had a mass in the left side of the scrotum for eighteen months. The mass was removed entirely, and at the time of the operation it was demonstrated that this did not arise in connection with a hernia, the tunica vaginalis, the epididymis or the testicle. The growth was composed of three closely related neoplasms, each distinct, grossly and histologically.

URETHRA

Rupture.—Silverstone [58] states that ruptures of the urethra usually occur in the male. Ruptures may be complete, involving the whole circumference or incomplete, involving a segment only or the mucosa only.

Treatment of ruptures of the urethra is by no means standardized. The majority of surgeons subscribe to certain principles of treatment: (1) diversion of the urine from the traumatized region; (2) reconstruction of the urethral channel; (3) maintenance of the caliber of the urethra during healing and during a variable postoperative period.

Many surgeons still deal with a complete rupture of the anterior portion of the urethra by perineal operation only. There is no doubt that preliminary suprapubic cystostomy renders the finding of the proximal end of the urethra a simple matter. Except when suture is impossible, it is not necessary to leave a catheter as a splint. When urine drains along the catheter, urethritis is inevitable and formation of stricture likely.

Rupture of the urethra should be dealt with at the time of injury. To postpone this until a later date would be to subject the patient to a second operation, perineal section with excision of scar tissue and repair of the urethra, which could always be done for stricture of the urethra if it had formed as a result of the primary operation. It is further suggested that suprapubic cystostomy, which helps with the localization of the proximal end of the urethra, then should be used for the purpose of diversion of the urinary stream.

TREATMENT WITH SULFONAMIDE COMPOUNDS

Finland, Peterson and Goodwin [59] report the results of treatment with sulfadiazine in 460 cases of a variety of infections. The earlier conclusion (at which time 446 other cases were reported) concerning the efficacy and low toxicity of sulfadiazine has been confirmed and extended.

The additional data which these authors present suggest that sulfadiazine may be accepted as the drug of choice in all cases of hemolytic streptococcic infections and for all of the various acute bacterial meningitides.

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56. Strong, G. H.: Lipomyxoma of the Spermatic Cord: Case Report and Review of Literature, J. Urol. **48**:527-532 (Nov.) 1942.

57. Marshall, V. F.: Tumor of Spermatic Cord: Report of Case, J. Urol. **48**:524-526 (Nov.) 1942.

58. Silverstone, M.: Traumatic Rupture of the Urethra, Brit. J. Surg. **30**:70-74 (July) 1942.

59. Finland, M.; Peterson, O. L., and Goodwin, R. A., Jr.: Sulfadiazine: Further Clinical Studies of Its Efficacy and Toxic Effects in Four Hundred and Sixty Patients, Ann. Int. Med. **17**:920-934 (Dec.) 1942.

The accumulated clinical results in the cases of acute gonococcic and staphylococcic infections and of acute infections of the urinary tract suggest that the efficacy of sulfadiazine in most cases of such infections is probably similar to that of sulfathiazole. Because of its lower toxicity, however, sulfadiazine may be considered to be the drug of choice, particularly when prolonged therapy is desirable.

Toxic effects attributable to sulfadiazine in this series were relatively few and mild. The comparatively frequent occurrence of complications in the urinary tract warrants the exercise of caution in the control of the dosage of the drug in relation to the intake and output of fluid. Caution is particularly essential for old persons, for patients with hypertension and for every patient who may have some impairment of renal function. With adequate control, this drug may be administered so that it produces therapeutically effective blood levels whenever indicated, even in many cases of severe renal disease. When oliguria occurs, the intake of fluid should be increased promptly or the dose of the drug reduced, depending on the circumstances. When there is marked or complete suppression of the output of urine, particularly if this is accompanied by ureteral pain, fluids should be forced and ureteral catheterization should be employed early if a fatal outcome is to be avoided. A fatal case of urinary suppression with ureteral colic, hematuria and azotemia is reported.

The occurrence of granulocytopenia after prolonged therapy in 1 case suggests that, regardless of how infrequent this complication may be, it must be looked for in all patients undergoing treatment with sulfadiazine for two weeks or more. Early recognition, with prompt withdrawal of the drug, will probably prevent fatalities from this complication.

Full courses of sulfadiazine were used for a considerable number of patients who previously had been treated with other sulfonamide compounds. The toxic effects from sulfadiazine in these cases were apparently similar in frequency and in all other respects to those encountered in cases in which there had not been any previous experience with other sulfonamide compounds. This was true regardless of whether or not the other drugs had produced toxic effects.

No evidence of "sensitization" was noted in any of the 21 cases in which a second or third course of sulfadiazine was given. In most of these cases full doses were used for a week or more each time. In some of them one or more courses of other sulfonamide drugs had been given also, with or without toxic effects. The possibility of sensitization, however, has not been excluded.

Greene, Pool and Cook [60] gave sulfadiazine in 42 clinical cases of infections of the urinary tract of varying degree due to a number of organisms in order to compare the drug with the other commonly used sulfonamide compounds. Fifty-seven per cent of the group of patients were considered cured and 29 per cent improved; 14 per cent were not improved and the results were classed as failures. The drug was of little value in the presence of urinary calculi, urinary retention or deep-seated pathologic changes. The results in the treatment of gonorrhea were promising. Approximately 3 Gm. of the drug was given daily in divided doses. The disagreeable side effects noted were less frequent and less severe than those which occur when the other sulfonamide compounds are employed. These authors are of the opinion that sulfadiazine is slightly less effective and more expensive but less toxic than sulfathiazole.

60. Greene, L. F.; Pool, T. L., and Cook, E. N.: Sulfadiazine in the Treatment of Infections of the Urinary Tract, Proc. Staff Meet., Mayo Clin. **17**:510-511 (Sept. 23) 1942.

Wright and Kinsey [61] report that 7 of 38 patients given sulfadiazine had renal complications. The amount of the drug, the concentration in the blood, the duration of the therapy, the intake of fluid and the urinary output are not the only factors involved in renal complications from sulfadiazine therapy. The urinary output was relatively low in comparison with the intake of fluid in the cases studied. This was one of the most constant findings in the 7 cases in which complications occurred. Renal tenderness was present in all 7 cases of renal complications and may prove a valuable warning sign. The finding of even a few erythrocytes, with or without crystals, in the urine is an indication that the drug should be withdrawn. There are probably two types of renal damage, one due to mechanical blockage and the other similar to poisoning from mercury bichloride. In most cases renal complications from sulfadiazine therapy will respond to conservative measures if they are instituted early. The purpose of these comments is not to decry the use of this valuable therapeutic agent but to emphasize the assiduous vigilance that is necessary to assure the safety of its use, particularly in the torrid climates and during the hot summer months in the temperate zone.

Louria and Solomon [62] report a case of anuria caused by sulfadiazine. The patient was a woman aged 25 years who had rheumatic heart disease. Therapy consisted of administration of sulfapyridine for twenty-four hours and later sulfadiazine. After five days of apparent tolerance to sulfadiazine, during which time there was no effect on the fever, the patient voided only 150 cc. of urine. Use of the drug was stopped immediately, but complete anuria was present all through the following day. The concentration of the drug in the blood on the day that its use was discontinued was 22.4 mg. per hundred cubic centimeters. A crystalline deposit was seen in the right ureteral orifice at cystoscopy. After irrigation of the right renal pelvis with warm saline solution, a slight, moderately active flow of urine appeared. Irrigation of the left renal pelvis with warm saline solution was necessary also to obtain a flow of urine. The catheters on both sides were left in place for seventy hours. These authors conclude that if the output of urine is good the presence of crystals in the voided urine should not be considered an indication for discontinuing use of the drug. The appearance of gross blood in the urine at any time during administration of the drug should be an indication for discontinuing its use. Hematuria clears up promptly after administration of the drug has been stopped. No permanent renal damage has been observed in the cases in which recovery has been reported. Obstruction of the urinary tract resulting from the deposition of crystals of the drug may be relieved promptly by ureteral catheterization and pelvic lavage. Whether alkalinization of the urine will prevent deposition of crystals in the urinary tract is still a moot point.

Greenwald [63] reviews the cases of patients with chancroidal infection admitted to the genitourinary disease service, Station Hospital, Fort Belvoir, Va., during a period of nine months.

Usually an incubation period of three to twelve days elapses before the onset of the ulcerations. Clinically, chancroid infection manifests itself as irregular, nonindurated ulcers with a granular, dirty grayish base, covered with a small amount of grayish purulent discharge. The edges are slightly undermined and irregular. The base bleeds easily on manipulation. Most of the chancroidal ulcers

61. Wright, D. O., and Kinsey, R. E.: Renal Complications Due to Sulfadiazine, J. A. M. A. **120**:1351-1354 (Dec. 26) 1942.

62. Louria, A. L., and Solomon, C.: Complete Anuria Caused by Sulfadiazine, J. A. M. A. **120**:1354-1356 (Dec. 26) 1942.

63. Greenwald, E.: Chancroidal Infection, J. A. M. A. **121**:9-11 (Jan. 2) 1943.

appear at the edge of a phimotic prepuce or, in circumcised males, on the frenum and in the coronal sulcus.

In this series Greenwald has found a chancroidal lesion coincident with syphilis in 10 instances. These cases presented no problem in therapy, however, for no adverse reaction marked the simultaneous use of sulfathiazole and daily full doses of mapharsen as used in the treatment of primary syphilis.

Once the diagnosis of Ducrey infection is made, Greenwald's routine consists in the administration of sulfathiazole in 4 Gm. daily doses, the initial dose being 2 Gm. These doses of the drug are continued for a minimum of seven days, with careful observation for toxic phenomena. In no case in this series was there indication for withdrawal of the drug because of toxicity. After a minimum of four dark field examinations, with negative results, in the intervals between which local application of dressings wet with saline solution was used, the lesions were treated twice daily with soaks in 1 : 8,000 potassium permanganate solution followed by application of sulfanilamide powder.

Helmholz [64] studied the effect of the commonly used sulfonamide compounds, namely, sulfathiazole, sulfadiazine, sulfacetimide (acetylsulfanilamide) and sulfapyridine, on a large number of strains of the bacteria isolated from urinary infections. Sulfathiazole acts bacteriostatically in lower concentrations (0.5 to 2.0 mg. per hundred cubic centimeters) than the other three compounds on the most frequently found organism, Escherichia coli. Except in the case of one resistant strain, sulfadiazine, sulfacetimide and sulfapyridine in concentrations of 50 mg. per hundred cubic centimeters completely inhibited the growth of Staphylococcus aureus. Of the 5 organisms studied with varying concentrations of the sulfonamide compounds, Pseudomonas aeruginosa was found to be the most resistant, followed in order by Proteus ammoniae, Staphylococcus aureus, Aerobacter aerogenes and various strains of Salmonella. Sulfapyridine did not exhibit the bacteriostatic properties of the other sulfonamide compounds and sulfathiazole was superior to the others in lower concentrations. Sulfathiazole seems to have the greater bacteriostatic action on a mixture of organisms.

Loveless and Denton [65] discuss the oral use of sulfathiazole in prophylaxis for gonorrhea. Sulfathiazole was given in doses of 2 Gm. as a prophylactic measure to a company of 1,400 Negroes before they left the fort on pass. Those taking station prophylaxis received no further drug. All others received an additional 4 Gm., 2 on returning to the fort and 2 the next morning. In this company a phenomenal disappearance of gonorrhea and chancroid occurred. If the men for whom this prophylactic measure failed who were not under the influence of the drug at the time of exposure are excluded, the gonorrhea rate dropped to a level of 8 per thousand yearly, as compared with 171 per thousand in the control group, and the chancroid rate dropped to 6, as compared with 52 in the control group.

UROLOGIC SURGERY

Priestley, Walters and Counseller [66] gave a report of urologic surgery carried out at the Mayo Clinic in 1941. In the entire group of 956 patients who were

64. Helmholz, H. F.: The Bacteriostatic Action of Sulfadiazine, Sulfathiazole, Sulfacetimide and Sulfapyridine on Bacteria Isolated from Urinary Infections, Proc. Staff Meet., Mayo Clin. **17**:529-533 (Oct. 21) 1942.

65. Loveless, J. A., and Denton, W.: The Oral Use of Sulfathiazole as a Prophylaxis for Gonorrhea, J. A. M. A. **121**:827-828 (March 13) 1943.

66. Priestley, J. T.; Walters, W., and Counseller, V. S.: Report of Urologic Surgery for 1941, Proc. Staff Meet., Mayo Clin. **17**:603-605 (Dec. 16) 1942.

treated surgically, only 6 deaths occurred, a mortality rate of 0.6 per cent. This is the most favorable mortality rate ever attained at the Mayo Clinic in the care of these patients. Many factors undoubtedly contributed to this mortality rate, including improvements in preoperative and postoperative care.

Of the various operations performed in 1941, operations were performed on the kidney in 334 cases with 5 deaths, a mortality rate of 1.5 per cent. In the majority of surgical cases of nephrolithiasis a conservative operation was performed, as nephrectomy is necessary in only approximately 1 of 4 of these cases. This is in contrast with the surgical cases of hydronephrosis, as in this group nephrectomy was performed in approximately 2 of 3 cases. During the past five years hydronephrosis has been treated surgically in 246 cases with no deaths. Renal tuberculosis was seen much less commonly in 1941 than in former years. Malignant tumors of the kidney compose an important group of lesions for which nephrectomy is required. Virtually all solid renal neoplasms of clinical significance are malignant. Approximately 80 per cent are adenocarcinomas or hypernephromas, 9 per cent epitheliomas, 5 per cent sarcomas, 5 per cent Wilms tumors and the remainder unusual types of lesions. During 1941 nephrectomy was performed in a total of 204 cases with 2 deaths. During 1941, according to Priestley and his associates, operations on the ureter were performed in 73 cases with 1 death at the Mayo Clinic. Ureterolithotomy was performed in 36 cases, and 1 death occurred in this group. Cases in which ureteral transplantation has been required have been of particular interest. During 1941 bilateral ureterosigmoidostomy was performed in 22 cases without a death. In 15 of these cases simultaneous bilateral ureterosigmoidostomy was carried out. During the past few years, several things have been learned regarding ureteral transplantation: (1) that proper preoperative preparation and postoperative care are extremely important; (2) that both ureters can be transplanted simultaneously without undue hazard, and (3) that the grossly abnormal ureter can be transplanted to the bowel in most instances with reasonable safety. In 11 of the 22 cases of bilateral ureterosigmoidostomy, carcinoma of the bladder was present. Cutaneous ureterotomy is an operation which is used infrequently and never from choice. In an exceptional case of advanced or complicated renal tuberculosis it may find a field of usefulness.

Surgical treatment of vesical lesions during 1941 was followed by results more gratifying than usual as 59 patients were operated on without a death. Twenty-seven of these 59 patients had malignant tumors. In 11 cases total cystectomy preceded by bilateral ureterosigmoidostomy was performed without a death. In 13 cases segmental resection of the bladder was carried out. During recent years interest in total cystectomy has grown materially. Priestley and his associates are of the opinion that as indications for treatment, preoperative preparation, surgical technic and postoperative care of vesical lesions become more standardized and thoroughly understood, indications for total cystectomy will become even broader. At present it is established that this procedure can be carried out with reasonable risk, and if cases are properly selected the ultimate prognosis should be more favorable than that associated with any other form of treatment for similar types of vesical carcinoma.

During 1941 orchidectomy was performed in 25 cases of carcinoma of the prostate gland. Priestley and his associates think that this form of treatment for prostatic carcinoma, suggested during recent years by Huggins, gives promise of being a great advance in the management of this condition. No patient had suprapubic or perineal operation for prostatic hypertrophy. During this same interval Thompson and his associates performed transurethral resection in 991 cases.

Eighty patients were treated for embryologic defects of the external genitalia, and testicular tumors were removed from 18.

Thompson, Emmett, Cook and Pool,[67] in discussing transurethral surgery at the Mayo Clinic in 1940 and 1941, state that in 1941 991 patients were subjected to transurethral resection of the prostate gland. Improvements in instruments and in technic, which have made it possible to apply the operation to many patients who were formerly denied relief of obstructive urinary symptoms, account in part for the increased number of patients coming to operation. The universal application of transurethral prostatic resection is indicated by the fact that during 1941 not a single patient was treated by perineal or suprapubic prostatectomy at the clinic.

The average age of the patients in this series was 66.2 years. Eighty-five (4.3 per cent) were 80 years of age or older. Only 2 of the patients who were in their eighties died after operation, a fact which attests to the relative safety of the procedure. The great majority of the patients left the hospital on the fifth or sixth postoperative day or before that time. Review of the records showed that of the 1,967 patients undergoing prostatic operation in the last two years (1940 and 1941) only 13 (less than 1 per cent) required more than one month of hospitalization after the operation. The average postoperative stay of the entire group was seven and seven-tenths days.

The average amount of tissue resected has steadily increased throughout the past decade, so that in 1941, if cases in which the obstruction was caused by a bar or contracture are excluded, the average weight of tissue removed was 37.3 Gm. per case. More than 100 Gm. was resected in 9 cases (1 per cent). In both 1940 and 1941, one stage transurethral resection was done in more than 96 per cent of cases.

Prior to ten years ago, suprapubic cystostomy was a commonly used method of preparing patients for subsequent removal of the prostate gland. Thompson and his associates have long felt that with proper catheter technic almost any patient with disease of the prostate could be prepared for operation by drainage of the bladder through a urethral catheter. They state that this does not necessarily mean that an inlying catheter is always used. It is often good judgment to utilize intermittent catheterization or go ahead with the operation without preliminary vesical drainage of any type. The reasons for making the decision as to the type of preoperative treatment were considered too involved to include in their article. However, it is of interest that in not a single case in the two years was suprapubic cystostomy done prior to operation as the means of treating a patient who had renal insufficiency or who was intolerant to urethral drainage with a catheter.

Litholapaxy either with or without prostatic resection was performed in 131 cases in the two years. Thompson and his associates prefer to use the Bigelow type of lithotrite and evacuate the fragments through a large direct vision cystoscope.

Treatment of tumors of the bladder at the Mayo Clinic has been somewhat altered during the past two years, in that Priestley, Walters and Counseller have done a number of total cystectomies on patients suffering from tumors of a high grade of malignancy. In the majority of cases, however, particularly in cases of vesical tumors of low grade, transurethral removal has seemed to be the method of choice. It was used in 333 instances. Since multiple sittings were employed in some cases, this does not represent the number of patients. However, tumors were presumably completely removed by transurethral means in 139 cases in the two

67. Thompson, G. J.; Emmett, J. L.; Cook, E. N., and Pool, T. L.: Transurethral Surgery in 1940 and 1941, Proc. Staff Meet., Mayo Clin. **17**:621-624 (Dec. 30) 1942.

years. In many of these the growths were of a low grade papillary nature, and in relatively few cases were tumors of high grade malignancy thus treated. In 18 of the latter cases radon emanation seeds were implanted.

Removal of ureteral calculi by transurethral manipulation was attempted in 150 cases by Thompson and his associates in 1940 and 1941. They state that success in removal of ureteral calculi depends on a number of factors and that good judgment as to the management of any patient results only from considerable experience. Even then discouraging and disappointing results sometimes ensue after any type of manipulation in what should be an easy operation. Successful results were obtained in 95 per cent of 150 cases. In several cases rather sharp postoperative reactions complicated the procedure. The Councill and Johnson stone extractors were employed in the large majority of cases, and as a rule the stone was removed at the time of manipulation. To guard against reaction, urethral drainage with a catheter, as well as drainage of the bladder with a urethral catheter, was employed for the first two or three days after manipulation.

The mortality rate following transurethral prostatic resection is of considerable interest. In 1940 there were 16 deaths among 976 patients, or a mortality rate of 1.6 per cent. In 1941 there were 11 deaths among 991 patients, or a rate of 1.1 per cent.

Colby [68] reports cutaneous ureterostomy in 10 cases of active renal tuberculosis. Advanced disease was present in all cases. In many there was active tuberculosis of bone, genital lesions and probably other areas of unsuspected disease, although there were no active pulmonary lesions. Cutaneous ureterostomy entails little risk; no deaths resulted directly from the operation, although 1 patient died from a ruptured tuberculous ulcer of the small intestine before leaving the hospital. Simultaneous bilateral ureterostomy was done on 2 patients who had tuberculosis of both kidneys. Both died within a few months, and neither was particularly benefited while alive. Considerable benefit from the operation results in those patients whose remaining kidney was diseased after the removal of the opposite tuberculous kidney. With them intolerable symptoms referable to the bladder were relieved and the progress of renal damage lessened. Five such patients who were treated by ureterostomy are alive and useful. If the operative result is a rosette of ureteral mucous membrane projecting beyond the skin, there is reason to believe patients can live comfortably without catheters and that they may escape formation of stricture at the skin, even in the presence of active renal tuberculosis. If this is true, these patients can easily care for themselves without the nuisance of changing catheters, and the danger of pyelonephritis, secondary infections with urea-splitting bacteria and formation of stones is lessened. Cutaneous ureterostomy, as usually performed, holds no guarantee of a satisfactory junction of skin and ureter. It is the most effective method of relieving symptoms from the hopelessly infected tuberculous bladder.

UROLITHIASIS

Jewett, Sloan and Strong [69] discuss vitamin A deficiency and clinical urolithiasis. The rate of dark adaptation and the thresholds of the completely dark-adapted eye were determined for 20 patients with urolithiasis and compared with those of 40 normal subjects. In addition the vitamin A content in the blood of these patients with urolithiasis was determined and compared with that of 33 normal

68. Colby, F. H.: Cutaneous Ureterostomy in Active Renal Tuberculosis, J. Urol. **48:** 357-367 (Oct.) 1942.

69. Jewett, H. J.; Sloan, L. L., and Strong, G. H.: Does Vitamin A Deficiency Exist in Clinical Urolithiasis? A Clinical and Pathologic Study of Ninety-Eight Cases, J. A. M. A. **121:**566-568 (Feb. 20) 1943.

control subjects. In 78 cases of urolithiasis which came to necropsy the respiratory and urinary tracts were examined for the epithelial metaplasia characteristic of vitamin A deficiency. In none of the 98 cases studied was there any evidence of vitamin A deficiency. Although a vitamin A–free diet produces widespread epithelial changes which may lead to the formation of urinary calculi in experimental animals, as yet there is no positive proof that "subclinical" vitamin A deficiency is an etiologic factor in urolithiasis in man.

Flocks [70] reviewed the material at the University Hospitals (Iowa City) and found that there was no evidence of vitamin A deficiency as an associated factor in 100 cases of calcium urolithiasis. This tends to confirm the careful work of Jewett, who has proved conclusively that in cases of calcium urolithiasis there is no more vitamin A deficiency than in any comparable group of cases of some other disease. Flocks is in doubt as to whether the problem had been completely cleared up, in view of the fact that in most of the cases of stone in the urinary tract the picture that is seen at the time the patient is observed is an end result. It is not the picture at the time when the stone is actually forming, and it may well be that when the stone or nucleus started one of the initiating factors was vitamin A deficiency. This fits in with some of the experimental work done on animals. It fits in with the known rapid formation of small calculi in acutely ill, bedridden, vitamin-deficient persons. The further growth of these stones, however, has no relation to vitamin A deficiency, as Jewett and his co-workers have conclusively proved. Whether or not vitamin A deficiency is an important associated factor in the formation of the nucleus is, Flocks believes, still a question which can be answered only by providing some means of demonstrating whether or not the patients are deficient in vitamin A during the time of formation of the nucleus.

DISSOLUTION OF URINARY CALCULI

Suby, Suby and Albright [71] discuss the property of acid solutions in relation to irritability of the mucosa of the bladder. Rabbits were used in their experimental work. In all, about 80 tests were carried out on the bladders of rabbits with the various solutions. Physiologic solution of sodium chloride was used for the test solution, and in none of these tests was any bleeding evident in the outflowing solution. After the use of sodium citrate–citric acid solution, the returning fluid was slightly pink. The addition of magnesium to the sodium citrate–citric acid solution eliminated the irritability without reducing the effectiveness of the solution. These experiments were carried out with the idea of finding some solution which would aid in the dissolution of calculi in the urinary tract. The one which proved the most effective, as judged by its ability to dissolve calcium phosphate and by its lack of irritating effects on the rabbit's bladder, was as follows:

Citric acid (monohydrate)	32.3 Gm.
Magnesium oxide (anhydrous)	3.8 Gm.
Sodium carbonate (anhydrous)	4.4 Gm.
Distilled water to make	1,000 cc.

Barney [72] discusses the paper of Suby, Suby and Albright and mentions 2 cases in which renal stones were dissolved. The first patient had a recurrent staghorn calculus in the left kidney. The kidney showed poor function, and on the opposite side there was an atrophic kidney with a double pelvis, each half of which contained

70. Flocks, R., in discussion on Jewett, Sloan and Strong.[69]

71. Suby, H. I.; Suby, R. M., and Albright, F.: Properties of Organic Acid Solutions Which Determine Their Irritability to the Bladder Mucous Membrane and the Effect of Magnesium Ions in Overcoming this Irritability, J. Urol. **48**:549-559 (Nov.) 1942.

72. Barney, J. D., in discussion on Suby, Suby and Albright.[71]

a stone. The left kidney was exposed through a nephrolithotomy incision, as much of the stone removed as could be reached and a nephrostomy tube inserted. The kidney was irrigated with sodium citrate–citric acid solution, and the remaining fragments were completely dissolved. The second patient had large bilateral stones. The right kidney was exposed; the cortex was opened at the upper pole and a piece of stone removed. Into this cavity an open-ended mushroom catheter was sutured. The renal pelvis was then opened and a similar catheter sutured in place. In this way a through and through stream of the dissolving fluid was maintained. After a number of solutions had been used, levulinic acid was finally employed. No untoward reactions occurred, but its dissolving power was not as strong as that of the citric acid solution. After several weeks of irrigation, only small fragments of stone remained. Nothing was done to the stone in the opposite kidney.

Keyser [73] discusses the paper of Suby, Suby and Albright and states that following the lead of chemists who have determined the solubility factors of hydrogen ion concentration and magnesium, phosphate and citrate ions, numerous investigators have worked with various solutions in an effort to speed up dissolution of carbonate and phosphate stones, both in vitro and in the patient. Keyser states that as yet he has not given detailed accounts of the many efforts he has made in attempting to dissolve such calculi, with an unending variety of acids and ion combinations, but he has spoken of this frequently in generalities. One point has been emphasized, namely, that the solvent action of any solution on a dense stone is impeded by the organized matter which remains around the surface of the stone after the superficial salts are dissolved.

Keyser has studied the rate of dissolution of stones with citrate buffers, hexametaphosphate mineral acids and other solvents. The citrate mixture of Albright has been found most satisfactory, but, again, as soon as surface dissolution is effected, a gel-like envelope encompasses the stone and the dissolution process is slowed down.

Treating the calculus with ferments previous to the application of solvents was next tried, the hypothetic principle being that the enzyme might cause disintegration of the organic envelope. At least partial success in the test tube has been achieved. It was found that solutions of urease in 0.5 per cent strength applied for a brief time to calcium phosphate calculi would bring about remarkable acceleration of the dissolution, when they were irrigated in a special apparatus with Albright's citrate mixture. Thus a stone which under standard conditions of weight, composition and density would likely require twenty-four hours of irrigation to dissolve would disintegrate in one or two hours after being exposed to the urease solution for a short time. Rather paradoxically it was shown that prolonged treatment with urease solution would slow down the rate of dissolution.

Keyser has had but one clinical opportunity to apply this technic of dissolution of stones. He had two months previously removed a large stone of phosphatic composition from the left kidney of this patient, and nephrostomy had been done. She also had a right ureteral calculus, which had partly destroyed the right kidney. In addition she was the victim of a left hemiplegia. About six weeks after the operation calcific shadows of recurrring calculi appeared in the left kidney. Alternate application of 0.5 per cent urease solution and irrigation with the solvent mixture of Suby and his associates through the nephrostomy tube brought about complete dissolution of this calcareous material in five days, as revealed by the roentgen rays.

73. Keyser, L. D., in discussion on Suby, Suby and Albright.[71]

ANURIA

Mayo and Schlicke,[74] in discussing anuria after operations on the colon and rectum, state that prophylaxis is the most effective method of dealing with this condition. Care should be exercised at the operating table to avoid undue trauma to the ureters and bladder. Routine dissection of the ureters in pelvic operations is dangerous and unsound. After operation, the output of urine must be watched carefully. The most dangerous period is after the first week. Fluids intended for parenteral administration are withdrawn, because the patient seems to be doing well, and he is left to his own resources for intake of fluids. If the intake of fluid decreases at this stage, when post-traumatic edema is at its peak, anuria may occur. Great care should be used in the administration of sulfonamide compounds, especially to older patients who already have symptoms of obstruction.

At the first sign of diminishing urinary flow—and such signs unfortunately are frequently overlooked or attributed to improper charting—prompt action is required. After simple retention of urine has been ruled out by catheterization of the bladder, the most important thing is to find the cause. Since dehydration is usually the paramount factor, this should be remedied without delay. Aqueous solutions of dextrose afford the most readily available sources of water for renal excretion, particularly if hypertonic solutions are used. Theophylline with ethylenediamine is a valuable stimulant to a sluggish kidney. Studies of blood chemistry should be carried out to determine the degree of nitrogen retention present and the extent of disturbance of acid-base equilibrium. Acidosis or alkalosis should be corrected. A plain roentgenogram of the abdomen will reveal the presence of opaque calculi. A careful physical examination should be carried out to detect the presence of associated conditions. If routine measures do not restore urinary flow, cystoscopic examination should be carried out without delay. Ureteral obstruction usually can be relieved by catheterization, but if the obstruction is bilateral and impassable, nephrostomy must be performed. A stormy course with pain suggests an obstructive type of anuria. A history of chemotherapy is important. Many of the measures often employed are of doubtful value. Sweating and purging exhaust the patient, further deplete the body of fluids and electrolytes and fail to eliminate nitrogenous waste. Heat applied to the renal regions finds its greatest usefulness in the comfort which it may afford the patient. Surgical procedures, such as splanchnic block anesthesia, decapsulation and peritoneal dialysis, often serve only to precipitate death.

PYURIA

Braasch [75] states that pus cells found in the voided urine of the female patient are of little or no clinical significance. In such instances a specimen of urine obtained by catheter is necessary. Pus cells in the voided urine of the male patient are of greater clinical value, particularly if the two glass test is employed. It is of equal clinical importance to determine the presence and kind of bacteria in the urine. Intelligent treatment of pyuria is dependent on a knowledge of its bacteriologic aspects. Rough identification of the type of organisms present is possible by the simple method of Gram's staining of the urinary sediment.

Bacillary infection is observed in most cases. Colon bacilli and Aerobacter aerogenes are the organisms usually found. Mixed infection may be present; most

74. Mayo, C. W., and Schlicke, C. P.: Anuria After Operations on the Colon and Rectum, J. Urol. **48**:207-218 (Aug.) 1942.

75. Braasch, W. F.: The Clinical Significance and Treatment of Pyuria, Ann. Int. Med. **17**:943-951 (Dec.) 1942.

often it is caused by colon bacilli with Str. faecalis. Unless this fact is recognized, chemotherapy may fail. Renal tuberculosis is a frequent cause of pyuria which resists chemotherapy. In recent years the symptoms and severity of the infection caused by renal tuberculosis have become milder and the recognition of such tuberculosis often is difficult.

Pyuria may be coincident with lesions situated in other organs. Acute cholecystitis coincident with pyuria often is observed. When a lesion requiring surgical attention is present, the question might arise: Would urinary infection interfere with operation? As a rule it does not, but a search should be made for the cause of the pyuria. A careful search for foci of infection and removal of them are always necessary. Pyuria or a history of previous infection of the urinary tract occurring with hypertension should be the guide to complete urologic investigation. In the presence of pyuria important clinical data can be obtained by such simple tests as the making of roentgenograms and excretory urograms.

Intelligent chemotherapy depends on identification of the bacteria. In cases in which the situation is complicated, infection caused by Escherichia coli often responds to treatment with mandelic acid. Of the sulfonamide compounds, sulfathiazole and sulfadiazine probably are preferable. Experience has shown that an initial daily dose of 3 or 4 Gm. is all that is necessary against most uncomplicated infections in the urinary tract. In fact, the effective dosage is gradually being reduced, and in most cases an initial dose of 3 Gm. daily for two days is being replaced by one of 2 Gm. administered for a period of six or eight days. When such a low dose is employed, the severe reactions to sulfonamide compounds described by those who employ them in treating profound systemic infections are seldom seen. Urologists have the advantage that the infected field is immersed in fluid containing the sulfonamide compound as is also the surrounding zone of reaction in the tissues, although the latter is the predominating factor. In contrast to the procedure in the treatment of systemic infection with a sulfonamide compound, it seldom is necessary to determine the concentration of the drug in the blood in treating infection of the urinary tract, since this concentration is low and does not exert much influence so far as results are concerned.

The danger of acetylation with deposition of crystals and the occurrence of anuria must be considered. Although there is a difference in the degree of acetylation caused by the various sulfonamide compounds, they all may be guilty of renal blockage. The degree of subjective toxic reaction which results is no criterion. The drug which causes the least symptomatic reaction (sulfadiazine) is one of the worst offenders in this respect. Anuria associated with the use of sulfadiazine demands the immediate cooperation of the urologist. By the introduction of ureteral catheters and lavage of the ureters and the renal pelves, the blockage usually can be relieved. It is obviously advisable to start such treatment in the early stages of anuria. Crystallization otherwise may become so dense that lavage is futile and injury to the renal cells may be fatal.

Persistent pyuria in spite of chemotherapy usually is caused by some underlying pathologic lesion in the urinary tract which requires careful examination and treatment by the urologist.

OSTEITIS PUBIS

Kleinberg [76] reports the case of a woman who had pubic osteitis due probably to the colon group of bacilli. The lesion resembles in many of its features the disease commonly seen in men as a sequel of a suprapubic prostatectomy. This case

76. Kleinberg, S.: Osteitis Pubis, with a Report of a Case in a Woman, J. Urol. **48**:635-641 (Dec.) 1942.

makes the third one thus far described in women and for this reason is unusual, since most of the patients have been men. The temperature range was higher than in the average case, but it is difficult to say whether this was due to the pubic osteitis or to the pyelonephritis. Presumably, however, the fever was caused by the osteitis, for it subsided promptly after the pelvis was immobilized.

PRIAPISM AND SICKLE CELL ANEMIA

Getzoff [77] discusses priapism and sickle cell anemia and reports 3 cases. He states that the mechanism of occurrence of thrombosis in the vascular system of the penis in cases of sickle cell anemia still awaits final acceptable explanation. A significant feature in the pathology of sickle cell anemia is the dilated capillaries, which are engorged with the abnormal cellular forms. Numerous instances of thrombosis and infarction in cases of sickle cell anemia have been reported in the literature to testify to the potential vascular complications of this blood dyscrasia. One theory to explain the mechanism of "sickling" is that the patient possesses an inheritable alteration in the hemopoietic system. The erythrocytes, unlike normal erythrocytes, absorb an unknown substance found in plasma. Although unanimity of opinion is lacking in regard to the etiology of sickle cell anemia, it may well be that each hypothesis will have contributed an integral share to the ultimate accepted facts. These theoretic considerations of sickle cell anemia have been applied to the clinical problem of priapism in an endeavor to bridge these two important entities.

When a prolonged erection is maintained, a reduction of venous return is associated with the engorgement of the cavernous bodies. The subsequent effect of this relatively sluggish status of the vascular bed of the penis may be a lowering of the oxygen tension and a temporary local reduction in the p_H of the blood and the release of those hematologic factors which influence sickling. An unusual cohesive attraction and tendency to formation of rouleaux may occur among sickle cells in the presence of relative stasis. If such large scale cellular aggregate formations and agglutination actually take place, the modus operandi of thrombus formation is set in motion. The thrombi act to occlude some of the vascular channels concerned with the venous return from the penis; further stasis occurs. A vicious cycle comes into play, and priapism ultimately takes place.

GRANULOMA INGUINALE

Tomskey, Vickery and Getzoff [78] discuss the treatment of 102 patients with granuloma inguinale and evaluate the various modern accepted methods of treatment. The latter are contrasted with a new mode of therapy which consists of local application of 20 per cent resin of podophyllum U. S. P. in olive oil and scarlet red ointment. The prolonged hospital stay and the too frequent futile endeavors to control the progress of the lesions of granuloma inguinale with antimony and potassium tartrate alone or with these drugs and surgical procedures have proved these therapeutic methods to be relatively ineffectual as compared with the results obtained with resin of podophyllum. The therapeutic value of resin of podophyllum for granuloma inguinale is emphasized by the fact that permanent cures have been attained with this drug, a result which previously has never been obtained in Tomskey, Vickery and Getzoff's experience.

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77. Getzoff, P. L.: Priapism and Sickle Cell Anemia: A Report of Three Cases, J. Urol. **48**:407-411 (Oct.) 1942.

78. Tomskey, G. C.; Vickery, G. W., and Getzoff, P. L.: The Successful Treatment of Granuloma Inguinale, with Special Reference to the Use of Podophyllin, J. Urol. **48**:401-406 (Oct.) 1942.